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(54) Title: (-)-2-[1-(3-ETHOXY-4-METHOXYPHENYL)-2-METHYLSULFONYLETHYL]-4-ACETYLAMINOISOINDOLINE-1,3-DIONE: METHODS OF USING AND COMPOSITIONS THEREOF

(57) Abstract: Stereomerically pure (-)-2-[1-(3-Ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminooindoline-1,3-dione, substantially free of its (+) isomer, and prodrugs, metabolites, polymorphs, salts, solvates, hydrates, and clathrates thereof are discussed. Also discussed are methods of using and pharmaceutical compositions comprising the (-) enantiomer of 2-[1-(3-Ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminooindoline-1,3-dione are disclosed. The methods include methods of treating and/or preventing disorders ameliorated by the reduction of levels of TNF- α or the inhibition of PDE4.

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**(-)-2-[1-(3-ETHOXY-4-METHOXYPHENYL)-
2-METHYLSULFONYLETHYL]-4-ACETYLAMINOISOINDOLINE-1,3-DIONE:
METHODS OF USING AND COMPOSITIONS THEREOF**

5 **1. FIELD OF INVENTION**

The invention relates to methods of using and compositions comprising the (-) enantiomer of 2-[1-(3-Ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione.

10 **2. BACKGROUND OF THE INVENTION**

Tumor necrosis factor alpha, (TNF- α) is a cytokine that is released primarily by mononuclear phagocytes in response to immunostimulators. TNF- α is capable of enhancing most cellular processes, such as differentiation, recruitment, proliferation, and proteolytic degradation. At low levels, TNF- α confers protection against infective agents, 15 tumors, and tissue damage. But TNF- α also has a role in many diseases. When administered to mammals or humans, TNF- α causes or aggravates inflammation, fever, cardiovascular effects, hemorrhage, coagulation, and acute phase responses similar to those seen during acute infections and shock states. Enhanced or unregulated TNF- α production has been implicated in a number of diseases and medical conditions, for example, cancers, 20 such as solid tumors and blood-born tumors; heart disease, such as congestive heart failure; and viral, genetic, inflammatory, allergic, and autoimmune diseases.

Adenosine 3',5'-cyclic monophosphate (cAMP) also plays a role in many diseases and conditions, such as but not limited to asthma and inflammation, and other conditions (Lowe and Cheng, *Drugs of the Future*, 17(9), 799-807, 1992). It has been 25 shown that the elevation of cAMP in inflammatory leukocytes inhibits their activation and the subsequent release of inflammatory mediators, including TNF- α and NF- κ B. Increased levels of cAMP also leads to the relaxation of airway smooth muscle.

It is believed that the primary cellular mechanism for the inactivation of cAMP is the breakdown of cAMP by a family of isoenzymes referred to as cyclic nucleotide phosphodiesterases (PDE) (Beavo and Reitsnyder, *Trends in Pharm.*, 11, 150-155, 1990). 30 There are eleven known PDE families. It is recognized, for example, that the inhibition of PDE type IV is particularly effective in both the inhibition of inflammatory mediator release and the relaxation of airway smooth muscle (Verghese, *et al.*, *Journal of Pharmacology and Experimental Therapeutics*, 272(3), 1313-1320, 1995). Thus, compounds that inhibit PDE4 35 (PDE IV) specifically, may inhibit inflammation and aid the relaxation of airway smooth muscle with a minimum of unwanted side effects, such as cardiovascular or anti-platelet

effects. Currently used PDE4 inhibitors lack the selective action at acceptable therapeutic doses.

Cancer is a particularly devastating disease, and increases in blood TNF- α levels are implicated in the risk of and the spreading of cancer. Normally, in healthy 5 subjects, cancer cells fail to survive in the circulatory system, one of the reasons being that the lining of blood vessels acts as a barrier to tumor-cell extravasation. But increased levels of cytokines have been shown to substantially increase the adhesion of cancer cells to endothelium in vitro. One explanation is that cytokines, such as TNF- α , stimulate the biosynthesis and expression of a cell surface receptors called ELAM-1 (endothelial 10 leukocyte adhesion molecule). ELAM-1 is a member of a family of calcium-dependent cell adhesion receptors, known as LEC-CAMs, which includes LECAM-1 and GMP-140. During an inflammatory response, ELAM-1 on endothelial cells functions as a "homing 15 receptor" for leukocytes. Recently, ELAM-1 on endothelial cells was shown to mediate the increased adhesion of colon cancer cells to endothelium treated with cytokines (Rice *et al.*, 1989, *Science* 246:1303-1306).

Inflammatory diseases such as arthritis, related arthritic conditions (e.g., osteoarthritis and rheumatoid arthritis), inflammatory bowel disease (e.g., Crohn's disease and ulcerative colitis), sepsis, psoriasis, and chronic obstructive pulmonary diseases, chronic inflammatory pulmonary diseases are also prevalent and problematic ailments. 20 TNF- α plays a central role in the inflammatory response and the administration of their antagonists block chronic and acute responses in animal models of inflammatory disease.

Enhanced or unregulated TNF- α production has been implicated in viral, genetic, inflammatory, allergic, and autoimmune diseases. Examples of such diseases include but are not limited to: HIV; hepatitis; adult respiratory distress syndrome; 25 bone-resorption diseases; chronic obstructive pulmonary diseases; chronic pulmonary inflammatory diseases; asthma, dermatitis; cystic fibrosis; septic shock; sepsis; endotoxic shock; hemodynamic shock; sepsis syndrome; post ischemic reperfusion injury; meningitis; psoriasis; fibrotic disease; cachexia; graft rejection; auto-immune disease; rheumatoid spondylitis; arthritic conditions, such as rheumatoid arthritis and osteoarthritis; 30 osteoporosis; Crohn's disease; ulcerative colitis; inflammatory-bowel disease; multiple sclerosis; systemic lupus erythematosus; ENL in leprosy; radiation damage; asthma; and hyperoxic alveolar injury. Tracey *et al.*, 1987, *Nature* 330:662-664 and Hinshaw *et al.*, 1990, *Circ. Shock* 30:279-292 (endotoxic shock); Dezube *et al.*, 1990, *Lancet*, 335:662 (cachexia); Millar *et al.*, 1989, *Lancet* 2:712-714 and Ferrai-Baliviera *et al.*, 1989, *Arch. 35 Surg.* 124:1400-1405 (adult respiratory distress syndrome); Bertolini *et al.*, 1986, *Nature*

319:516-518, Johnson *et al.*, 1989, *Endocrinology* 124:1424-1427, Holler *et al.*, 1990, *Blood* 75:1011-1016, and Grau *et al.*, 1989, *N. Engl. J. Med.* 320:1586-1591 (bone resorption diseases); Pignet *et al.*, 1990, *Nature*, 344:245-247, Bissonnette *et al.*, 1989, *Inflammation* 13:329-339 and Baughman *et al.*, 1990, *J. Lab. Clin. Med.* 115:36-42 (chronic pulmonary inflammatory diseases); Elliot *et al.*, 1995, *Int. J. Pharmacol.* 17:141-145 (rheumatoid arthritis); von Dullemen *et al.*, 1995, *Gastroenterology*, 109:129-135 (Crohn's disease); Duh *et al.*, 1989, *Proc. Nat. Acad. Sci.* 86:5974-5978, Poll *et al.*, 1990, *Proc. Nat. Acad. Sci.* 87:782-785, Monto *et al.*, 1990, *Blood* 79:2670, Clouse *et al.*, 1989, *J. Immunol.* 142, 431-438, Poll *et al.*, 1992, *AIDS Res. Hum. Retrovirus*, 191-197, Poli *et al.* 1990, *Proc. Natl. Acad. Sci.* 87:782-784, Folks *et al.*, 1989, *PNAS* 86:2365-2368 (HIV and opportunistic infections resulting from HIV).

5 Pharmaceutical compounds that can block the activity or inhibit the production of certain cytokines, including TNF- α , may be beneficial therapeutics. Many small-molecule inhibitors have demonstrated an ability to treat or prevent inflammatory 10 diseases implicated by TNF- α (for a review, see Lowe, 1998 *Exp. Opin. Ther. Patents* 8:1309-1332). One such class of molecules are the substituted phenethylsulfones described in United States patent number 6,020,358.

3. SUMMARY OF THE INVENTION

20 This invention relates to methods of treating diseases and disorders utilizing an enantiomer of a substituted phenethylsulfone compound and pharmaceutically acceptable salts, hydrates, solvates, clathrates, prodrugs and polymorphs thereof and methods for reducing the level of cytokines and their precursors in mammals. The invention also relates to pharmaceutical compositions comprising an enantiomer of 2-[1-(3-Ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione and a 25 pharmaceutically acceptable carrier. The invention further relates to an enantiomer of 2-[1-(3-Ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione substantially free of its other enantiomer.

This invention particularly relates to the (-) enantiomer of 2-[1-(3-Ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione. This 30 compound is believed to have increased potency and other benefits as compared to its racemate -- 2-[1-(3-Ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione.

The invention encompasses the use of the (-) enantiomer of 2-[1-(3-Ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione for treating 35

or preventing diseases or disorders ameliorated by the inhibition of TNF- α production in mammals. To certain embodiments, this treatment includes the reduction or avoidance of adverse effects. Such disorders include, but are not limited to, cancers, including, but not limited to cancer of the head, thyroid, neck, eye, skin, mouth, throat, esophagus, chest, bone, 5 blood, bone marrow, lung, colon, sigmoid, rectum, stomach, prostate, breast, ovaries, kidney, liver, pancreas, brain, intestine, heart, adrenal, subcutaneous tissue, lymph nodes, heart, or combinations thereof. Specific cancers that can be treated by this method are multiple myeloma, malignant melanoma, malignant glioma, leukemia and solid tumors.

The invention also encompasses the use of the (-) enantiomer of 2-[1-(3-Ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione in 10 the treatment or prevention of heart disease, including, but not limited to congestive heart failure, cardiomyopathy, pulmonary edema, endotoxin-mediated septic shock, acute viral myocarditis, cardiac allograft rejection, and myocardial infarction.

The invention also encompasses the use of the (-) enantiomer of 2-[1-(3-Ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione to 15 treat diseases or disorders ameliorated by the inhibition of PDE4. For example, the compounds and compositions of the invention may be useful to treat or prevent viral, genetic, inflammatory, allergic, and autoimmune diseases. Examples of such diseases include, but are not limited to: HIV; hepatitis; adult respiratory distress syndrome; 20 bone-resorption diseases; chronic obstructive pulmonary diseases; chronic pulmonary inflammatory diseases; dermatitis; cystic fibrosis; septic shock; sepsis; endotoxic shock; hemodynamic shock; sepsis syndrome; post ischemic reperfusion injury; meningitis; psoriasis; fibrotic disease; cachexia; graft rejection including graft versus host disease; auto-immune disease; rheumatoid spondylitis; arthritic conditions, such as rheumatoid 25 arthritis and osteoarthritis; osteoporosis; Crohn's disease; ulcerative colitis; inflammatory-bowel disease; multiple sclerosis; systemic lupus erythematosus; erythema nodosum leprosum (ENL) in leprosy; radiation damage; asthma; and hyperoxic alveolar injury.

In yet another embodiment, the (-) enantiomer of 2-[1-(3-Ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione is also useful 30 in the treatment or prevention of microbial infections or the symptoms of microbial infections including, but not limited to, bacterial infections, fungal infections, malaria, mycobacterial infection, and opportunistic infections resulting from HIV.

The invention further encompasses pharmaceutical compositions and single 35 unit dosage forms comprising an enantiomer of 2-[1-(3-Ethoxy-4-methoxyphenyl)-2-

methylsulfonylethyl]-4-acetylaminooindoline-1,3-dione and pharmaceutically acceptable polymorphs, prodrugs, salts, hydrates, clathrates, and solvates thereof.

In a separate embodiment, the invention encompasses the (-) enantiomer of 2-[1-(3-Ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminooindoline-1,3-dione.

5

In a further embodiment, the invention encompasses a method of producing a stereomerically pure enantiomer of 2-[1-(3-Ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminooindoline-1,3-dione which comprises contacting 1-(3-Ethoxy-4-methoxy-phenyl)-2-methanesulfonyl-ethylamine with a chiral amino acid and 10 contacting the product of the first step with N-(1,3-Dioxo-1,3-dihydro-isobenzofuran-4-yl)-acetamide. In a related embodiment the invention encompasses a chiral salt of 1-(3-Ethoxy-4-methoxy-phenyl)-2-methanesulfonyl-ethylamine.

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3.1. BRIEF DESCRIPTION OF THE FIGURES

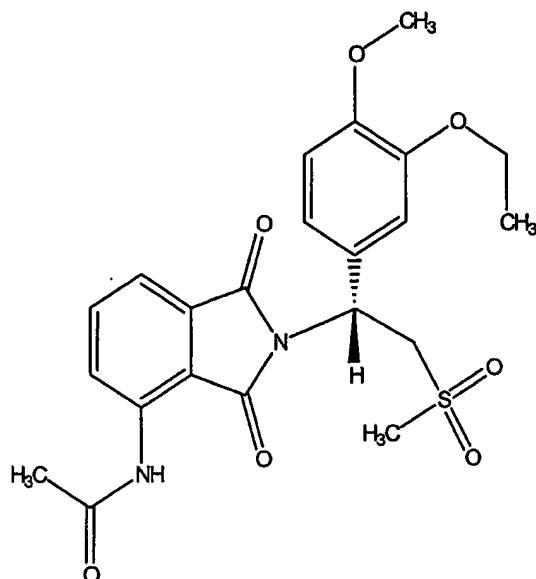
FIG 1. illustrates the preparation of the (-) enantiomer of 2-[1-(3-Ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminooindoline-1,3-dione.

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3.2. DEFINITIONS

As used herein, term "Compound A" refers to an enantiomerically pure form of 2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminooindoline-1,3-dione which comes off of an HPLC column at about 29.5 minutes when that column is a 150 mm x 4.6 mm Ultron Chiral ES-OVS chiral HPLC column (Agilent Technology), the eluent is 15:85 ethanol: 20 mM KH₂PO₄ at pH 3.5, and the observation wavelength is 240 nm. The ¹H NMR spectrum of Compound A is substantially as follows δ(CDCl₃): 1.47 (t, 3H), 2.26 (s, 3H), 2.87 (s, 3H), 3.68-3.76 (dd, 1H), 3.85 (s, 3H), 4.07-4.15 (q, 2H), 4.51-4.60 (dd, 1H), 5.84-5.90 (dd, 1H), 6.82-8.77 (m, 6H), 9.46 (s, 1H). The ¹³C NMR spectrum of Compound A is substantially as follows: δ(DMSO-d₆): 14.69, 24.95, 41.65, 48.58, 54.52, 55.95, 64.54, 111.48, 112.43, 115.13, 118.24, 120.31, 124.98, 129.25, 131.05, 136.13, 137.64, 148.66, 149.78, 167.50, 169.16, 169.52. Compound A, dissolved in 30 methanol, also rotates plane polarized light in the (-) direction.

Without being limited by theory, Compound A is believed to be R-{2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminooindoline-1,3-dione}, which has the following structure:



As used herein, the term "patient" refers to a mammal, particularly a human.

As used herein, the term "pharmaceutically acceptable salts" refer to salts prepared from pharmaceutically acceptable non-toxic acids or bases including inorganic acids and bases and organic acids and bases. Suitable pharmaceutically acceptable base addition salts for the compound of the present invention include metallic salts made from aluminum, calcium, lithium, magnesium, potassium, sodium and zinc or organic salts made from lysine, N,N'-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine (N-methylglucamine) and procaine. Suitable non-toxic acids 5 include, but are not limited to, inorganic and organic acids such as acetic, alginic, anthranilic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethenesulfonic, formic, fumaric, furoic, galacturonic, gluconic, glucuronic, glutamic, glycolic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pamoic, pantothenic, phenylacetic, phosphoric, propionic, salicylic, stearic, succinic, 10 sulfanilic, sulfuric, tartaric acid, and p-toluenesulfonic acid. Specific non-toxic acids include hydrochloric, hydrobromic, phosphoric, sulfuric, and methanesulfonic acids. 15 Examples of specific salts thus include hydrochloride and mesylate salts.

As used herein and unless otherwise indicated, the term "prodrug" means a derivative of a compound that can hydrolyze, oxidize, or otherwise react under biological 20 conditions (*in vitro* or *in vivo*) to provide the compound. Examples of prodrugs include, but

are not limited to, derivatives and metabolites of Compound A that include biohydrolyzable moieties such as biohydrolyzable amides, biohydrolyzable esters, biohydrolyzable carbamates, biohydrolyzable carbonates, biohydrolyzable ureides, and biohydrolyzable phosphate analogues. Prodrugs can typically be prepared using well-known methods, such 5 as those described by 1 *Burger's Medicinal Chemistry and Drug Discovery*, 172-178, 949-982 (Manfred E. Wolff ed., 5th ed. 1995).

As used herein and unless otherwise indicated, the terms "biohydrolyzable amide," "biohydrolyzable ester," "biohydrolyzable carbamate," "biohydrolyzable carbonate," "biohydrolyzable ureide," "biohydrolyzable phosphate" mean an amide, ester, carbamate, 10 carbonate, ureide, or phosphate, respectively, of a compound that either: 1) does not interfere with the biological activity of the compound but can confer upon that compound advantageous properties *in vivo*, such as uptake, duration of action, or onset of action; or 2) is biologically inactive but is converted *in vivo* to the biologically active compound. Examples of biohydrolyzable esters include, but are not limited to, lower alkyl esters, 15 alkoxyacyloxy esters, alkyl acylamino alkyl esters, and choline esters. Examples of biohydrolyzable amides include, but are not limited to, lower alkyl amides, α -amino acid amides, alkoxyacyl amides, and alkylaminoalkylcarbonyl amides. Examples of biohydrolyzable carbamates include, but are not limited to, lower alkylamines, substituted 20 ethylenediamines, aminoacids, hydroxyalkylamines, heterocyclic and heteroaromatic amines, and polyether amines.

As used herein and unless otherwise indicated, the term "stereomerically pure" means a composition that comprises one stereoisomer of a compound and is substantially free of other stereoisomers of that compound. For example, a stereomerically pure composition of a compound having one chiral center will be substantially free of the 25 opposite enantiomer of the compound. A stereomerically pure composition of a compound having two chiral centers will be substantially free of other diastereomers of the compound. A typical stereomerically pure compound comprises greater than about 80% by weight of one stereoisomer of the compound and less than about 20% by weight of other stereoisomers of the compound, more preferably greater than about 90% by weight of one 30 stereoisomer of the compound and less than about 10% by weight of the other stereoisomers of the compound, even more preferably greater than about 95% by weight of one stereoisomer of the compound and less than about 5% by weight of the other stereoisomers of the compound, and most preferably greater than about 97% by weight of one stereoisomer of the compound and less than about 3% by weight of the other stereoisomers 35 of the compound.

As used herein and unless otherwise indicated, the term "enantiomerically pure" means a stereomerically pure composition of a compound having one chiral center.

As used herein and unless otherwise indicated, "adverse effects" includes, but is not limited to gastrointestinal, renal and hepatic toxicities, leukopenia, increases in 5 bleeding times due to, *e.g.*, thrombocytopenia, and prolongation of gestation, nausea, vomiting, somnolence, asthenia, dizziness, teratogenicity, extra-pyramidal symptoms, akathisia, cardiotoxicity including cardiovascular disturbances, male sexual dysfunction, and elevated serum liver enzyme levels. The term "gastrointestinal toxicities" includes but is not limited to gastric and intestinal ulcerations and erosions. The term "renal toxicities" 10 includes but is not limited to such conditions as papillary necrosis and chronic interstitial nephritis.

As used herein and unless otherwise indicated, the phrases "reduce or avoid adverse effects" and "reducing or avoiding adverse effects" mean the reduction of the severity of one or more adverse effects as defined herein.

15 It should be noted that if there is a discrepancy between a depicted structure and a name given that structure, the depicted structure is to be accorded more weight. In addition, if the stereochemistry of a structure or a portion of a structure is not indicated with, for example, bold or dashed lines, the structure or portion of the structure is to be interpreted as encompassing all stereoisomers of it.

20

4. DETAILED DESCRIPTION OF THE INVENTION

This invention relates to stereomerically pure Compound A, which is an enantiomer of 2-[1-(3-Ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione, substantially free of its other enantiomer, as well as novel 25 methods using, and compositions comprising stereomerically pure Compound A. For example, the present invention encompasses the *in vitro* and *in vivo* use of Compound A, and the incorporation of Compound A into pharmaceutical compositions and single unit dosage forms useful in the treatment and prevention of a variety of diseases and disorders. Diseases and disorders which are ameliorated by the reduction of levels of TNF- α or 30 inhibition of PDE4 are well known in the art and are described herein. Specific methods of the invention reduce or avoid the adverse effects associated with compounds used as TNF- α inhibitor. Other specific methods of the invention reduce or avoid the adverse effects associated with use of racemic 2-[1-(3-Ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione.

Specific methods of the invention include methods of treating or preventing diseases and disorders including, but not limited to, solid tumor cancers, blood-born cancers and inflammatory diseases.

5 Pharmaceutical and dosage forms of the invention, which comprise Compound A or a pharmaceutically acceptable polymorph, prodrug, salt, clathrate, solvate or hydrate thereof, can be used in the methods of the invention.

Without being limited by theory, it is believed that Compound A can inhibit TNF- α production. Consequently, a first embodiment of the invention relates to a method of inhibiting TNF- α production which comprises contacting a cell exhibiting abnormal 10 TNF- α production with an effective amount of stereomerically pure Compound A, or a pharmaceutically acceptable prodrug, metabolite, polymorph, salt, solvate, hydrate, or clathrate thereof. In a particular embodiment, the invention relates to a method of inhibiting TNF- α production which comprises contacting a mammalian cell exhibiting abnormal 15 TNF- α production with an effective amount of stereomerically pure Compound A, or a pharmaceutically acceptable prodrug, metabolite, polymorph, salt, solvate, hydrate, or clathrate thereof.

The invention also relates to a method of treating or preventing disorders ameliorated by the reduction of levels of TNF- α in a patient which comprises administering 20 to a patient in need of such treatment or prevention a therapeutically or prophylactically effective amount of stereomerically pure compound A, or a pharmaceutically acceptable prodrug, metabolite, polymorph, salt, solvate, hydrate, or clathrate thereof.

A further embodiment of the invention relates to a method of treating or preventing cancer, including but not limited to, solid tumor, blood-born tumor, leukemias, and in particular, multiple myeloma in a patient which comprises administering to a patient 25 in need of such treatment or prevention a therapeutically effective amount of stereomerically pure compound A, or a pharmaceutically acceptable prodrug, metabolite, polymorph, salt, solvate, hydrate, or clathrate thereof; in particular wherein the patient is a mammal.

In another embodiment, the invention relates to a method of inhibiting PDE4 which comprises contacting PDE4 with an effective amount of stereomerically pure 30 Compound A, or a pharmaceutically acceptable prodrug, metabolite, polymorph, salt, solvate, hydrate, or clathrate thereof.

In another embodiment, the invention relates to a method of controlling cAMP levels in a cell which comprises contacting a cell with an effective amount of 35 stereomerically pure Compound A, or a pharmaceutically acceptable prodrug, metabolite, polymorph, salt, solvate, hydrate, or clathrate thereof. As used herein the term "controlling

cAMP levels" includes preventing or reducing the rate of the breakdown of Adenosine 3',5'-cyclic monophosphate (cAMP) in a cell or increasing the amount of Adenosine 3',5'-cyclic monophosphate present in a cell, preferably a mammalian cell, more preferably a human cell. In a particular method, the rate of cAMP breakdown is reduced by about 10, 5 25, 50, 100, 200, or 500 percent as compared to the rate in comparable cells which have not been contacted with a compound of the invention.

A further embodiment of the invention relates to a method of treating or preventing diseases or disorders ameliorated by the inhibition of PDE4 in a patient which comprises administering to a patient in need of such treatment or prevention a 10 therapeutically or prophylactically effective amount of stereomerically pure Compound A, or a pharmaceutically acceptable prodrug, metabolite, polymorph, salt, solvate, hydrate, or clathrate thereof. Disorders ameliorated by the inhibition of PDE4 include, but are not limited to, asthma, inflammation (e.g., inflammation due to reperfusion), chronic or acute 15 obstructive pulmonary diseases, chronic or acute pulmonary inflammatory diseases, inflammatory bowel disease, Crohn's Disease, Bechet's Disease, or colitis.

A further embodiment of the invention relates to a method of treating or preventing asthma, inflammation (e.g., contact dermatitis, atopic dermatitis, psoriasis, rheumatoid arthritis, osteoarthritis, inflammatory skin disease, inflammation due to reperfusion), chronic or acute obstructive pulmonary diseases, chronic or pulmonary 20 inflammatory diseases, inflammatory bowel disease, Crohn's Disease, Bechet's Disease or colitis in a patient which comprises administering to a patient in need of such treatment or prevention a therapeutically or prophylactically effective amount of stereomerically pure Compound A, or a pharmaceutically acceptable prodrug, metabolite, polymorph, salt, solvate, hydrate, or clathrate thereof; in particular wherein the patient is a mammal.

25 A separate embodiment of the invention encompasses methods of treating or preventing Myelodysplastic syndrome (MDS) which comprises administering to a patient in need of such treatment or prevention a therapeutically or prophylactically effective amount of stereomerically pure Compound A, or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, clathrate, or prodrug thereof. MDS refers to a diverse group of 30 hematopoietic stem cell disorders. MDS is characterized by a cellular marrow with impaired morphology and maturation (dysmyelopoiesis), peripheral blood cytopenias, and a variable risk of progression to acute leukemia, resulting from ineffective blood cell production. *See The Merck Manual 953 (17th ed. 1999) and List et al., 1990, J. Clin. Oncol. 8:1424.MDS*

A separate embodiment of the invention encompasses methods of treating or preventing Myeloproliferative disease (MPD) which comprises administering to a patient in need of such treatment or prevention a therapeutically or prophylactically effective amount of stereomerically pure Compound A, or a pharmaceutically acceptable salt, solvate, 5 hydrate, stereoisomer, clathrate, or prodrug thereof. Myeloproliferative disease (MPD) refers to a group of disorders characterized by clonal abnormalities of the hematopoietic stem cell. *See e.g.*, Current Medical Diagnosis & Treatment, pp. 499 (37th ed., Tierney et al. ed, Appleton & Lange, 1998).

The invention also encompasses a method of treating, preventing or 10 managing complex regional pain syndrome, which comprises administering to a patient in need of such treatment, prevention or management a therapeutically or prophylactically effective amount of a stereomerically pure Compound A, or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, clathrate, or prodrug thereof. In a specific embodiment, the administration is before, during or after surgery or physical therapy directed at reducing 15 or avoiding a symptom of complex regional pain syndrome in the patient.

In particular methods of the invention, stereomerically pure Compound A, or a pharmaceutically acceptable polymorph, prodrug, salt, solvate, hydrate, or clathrate thereof, is adjunctively administered with at least one additional therapeutic agent. Examples of additional therapeutic agents include, but are not limited to, anti-cancer drugs, 20 anti-inflammatories, antihistamines and decongestants.

4.1. SYNTHESIS AND PREPARATION

Racemic 2-[1-(3-Ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione is readily prepared from the methods in United States 25 Patent No. 6,020,358, which is incorporated herein by reference.

Compound A can be isolated from the racemic compound by techniques known in the art. Examples include, but are not limited to, the formation of chiral salts and the use of chiral or high performance liquid chromatography "HPLC" and the formation and crystallization of chiral salts. *See, e.g.*, Jacques, J., et al., *Enantiomers, Racemates and Resolutions* (Wiley-Interscience, New York, 1981); Wilen, S. H., et al., *Tetrahedron* 33:2725 (1977); Eliel, E. L., *Stereochemistry of Carbon Compounds* (McGraw-Hill, NY, 1962); and Wilen, S. H., *Tables of Resolving Agents and Optical Resolutions* p. 268 (E.L. Eliel, Ed., Univ. of Notre Dame Press, Notre Dame, IN, 1972).

In a specific method, Compound A can be synthesized from 35 3-acetamidophthalic anhydride and a chiral amino acid salt of

(R)-2-(3-ethoxy-4-methoxyphenyl)-1-(methylsulphonyl)-eth-2-ylamine. Chiral amino acid salts of (R)-2-(3-ethoxy-4-methoxyphenyl)-1-(methylsulphonyl)-eth-2-ylamine include, but not limited to salts formed with the D isomers of alanine, arginine, asparagine, aspartic acid, cysteine, glutamine, glutamic acid, glycine, histidine, isoleucine, leucine, lysine, 5 methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine, valine, ornithine, 4-aminobutyric acid, 2 amino isobutyric acid, 3 amino propionic acid, ornithine, norleucine, norvaline, hydroxyproline, sarcosine, citrulline, cysteic acid, t-butylglycine, t-butylalanine, phenylglycine, cyclohexylalanine, and N-acetyl-leucine. A specific chiral 10 amino acid salt is (S)-2-(3-ethoxy-4-methoxyphenyl)-1-(methylsulphonyl)-eth-2-ylamine N-acetyl-D-leucine salt, which is resolved from 2-(3-ethoxy-4-methoxyphenyl)-1-(methylsulphonyl)-eth-2-ylamine and N-acetyl-D-leucine in methanol.

4.2. METHODS OF TREATMENT

15 The invention encompasses methods of treating and preventing diseases or disorders ameliorated by the reduction of levels of TNF- α in a patient which comprise administering to a patient in need of such treatment or prevention a therapeutically effective amount of stereomerically pure Compound A, or a pharmaceutically acceptable prodrug, metabolite, polymorph, salt, solvate, hydrate, or clathrate thereof.

20 Disorders ameliorated by the inhibition of TNF- α include, but are not limited to: heart disease, such as congestive heart failure, cardiomyopathy, pulmonary edema, endotoxin-mediated septic shock, acute viral myocarditis, cardiac allograft rejection, and myocardial infarction; solid tumors, including but not limited to, sarcoma, carcinomas, fibrosarcoma, myxosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, chordoma, 25 angiosarcoma, endothelioma, lymphangiosarcoma, lymphangioendothelioma, synovioma, mesothelioma, Ewing's tumor, leiomyosarcoma, rhabdomyosarcoma, colon carcinoma, pancreatic cancer, breast cancer, ovarian cancer, prostate cancer, squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, sweat gland carcinoma, sebaceous gland carcinoma, papillary carcinoma, papillary adenocarcinomas, cystadenocarcinoma, medullary carcinoma, bronchogenic carcinoma, renal cell carcinoma, hepatoma, bile duct carcinoma, 30 choriocarcinoma, seminoma, embryonal carcinoma, Wilms' tumor, cervical cancer, testicular tumor, lung carcinoma, small cell lung carcinoma, bladder carcinoma, epithelial carcinoma, glioma, astrocytoma, medulloblastoma, craniopharyngioma, ependymoma, Kaposi's sarcoma, pinealoma, hemangioblastoma, acoustic neuroma, oligodendrogioma, 35 menangioma, melanoma, neuroblastoma, and retinoblastoma; and blood-born tumors

including but not limited to, acute lymphoblastic leukemia "ALL", acute lymphoblastic B-cell leukemia, acute lymphoblastic T-cell leukemia, acute myeloblastic leukemia "AML", acute promyelocytic leukemia "APL", acute monoblastic leukemia, acute erythroleukemic leukemia, acute megakaryoblastic leukemia, acute myelomonocytic leukemia, acute 5 nonlymphocytic leukemia, acute undifferentiated leukemia, chronic myelocytic leukemia "CML", chronic lymphocytic leukemia "CLL", hairy cell leukemia, multiple myeloma and acute and chronic leukemias, for example, lymphoblastic, myelogenous, lymphocytic, and myelocytic leukemias.

Specific methods of the invention further comprise the administration of an 10 additional therapeutic agent (*i.e.*, a therapeutic agent other than Compound A). Examples of additional therapeutic agents include, but are not limited to, anti-cancer drugs such as, but are not limited to: alkylating agents, nitrogen mustards, ethylenimines, methylmelamines, alkyl sulfonates, nitrosoureas, triazenes, folic acid analogs, pyrimidine analogs, purine 15 analogs, vinca alkaloids, epipodophyllotoxins, antibiotics, topoisomerase inhibitors and anti-cancer vaccines.

Specific additional therapeutic agents include, but are not limited to: 20 acivicin; aclarubicin; acodazole hydrochloride; acronine; adozelesin; aldesleukin; altretamine; ambomycin; ametantrone acetate; aminoglutethimide; amsacrine; anastrozole; anthramycin; asparaginase; asperlin; azacitidine; azetepa; azotomycin; batimastat; benzodepa; bicalutamide; bisantrene hydrochloride; bisnafide dimesylate; bizelesin; bleomycin sulfate; brequinar sodium; bropirimine; busulfan; cactinomycin; calusterone; caracemide; carbetimer; carboplatin; carmustine; carubicin hydrochloride; carzelesin; cedefingol; chlorambucil; cirolemycin; cisplatin; cladribine; crisnatol mesylate; cyclophosphamide; cytarabine; dacarbazine; dactinomycin; daunorubicin hydrochloride; 25 decitabine; dexormaplatin; dezaguanine; dezaguanine mesylate; diaziquone; docetaxel; doxorubicin; doxorubicin hydrochloride; droloxitene; droloxitene citrate; dromostanolone propionate; duazomycin; edatrexate; eflornithine hydrochloride; elsamitucin; enoplatin; enpromate; epipropidine; epirubicin hydrochloride; erbulazole; esorubicin hydrochloride; estramustine; estramustine phosphate sodium; etanidazole; etoposide; etoposide phosphate; 30 etoprine; fadrozole hydrochloride; fazarabine; fenretinide; floxuridine; fludarabine phosphate; fluorouracil; flurocitabine; fosquidone; fostriecin sodium; gemcitabine; gemcitabine hydrochloride; hydroxyurea; idarubicin hydrochloride; ifosfamide; ilmofosine; interleukin II (including recombinant interleukin II, or rIL2), interferon alfa-2a; interferon alfa-2b; interferon alfa-n1 ; interferon alfa-n3; interferon beta-I a; interferon gamma-I b; 35 iproplatin; irinotecan hydrochloride; lanreotide acetate; letrozole; leuprolide acetate;

liarozole hydrochloride; lometrexol sodium; lomustine; losoxantrone hydrochloride; masoprolol; maytansine; mechlorethamine hydrochloride; megestrol acetate; melengestrol acetate; melphalan; menogaril; mercaptopurine; methotrexate; methotrexate sodium; metoprine; meturedepa; mitindomide; mitocarcin; mitocromin; mitogillin; mitomalcin; 5 mitomycin; mitosper; mitotane; mitoxantrone hydrochloride; mycophenolic acid; nocodazole; nogalamycin; ormaplatin; oxisuran; paclitaxel; pegaspargase; peliomycin; pentamustine; peplomycin sulfate; perfosfamide; pipobroman; piposulfan; piroxantrone hydrochloride; plicamycin; plomestane; porfimer sodium; porfiromycin; prednimustine; procarbazine hydrochloride; puromycin; puromycin hydrochloride; pyrazofurin; riboprine; 10 roletimide; safingol; safingol hydrochloride; semustine; simtrazene; sparfosate sodium; sparsomycin; spirogermanium hydrochloride; spiromustine; spiroplatin; streptonigrin; streptozocin; sulofenur; talisomycin; tecogalan sodium; tegafur; teloxantrone hydrochloride; temoporfin; teniposide; teroxirone; testolactone; thiamiprime; thioguanine; thiotepea; tiazofurin; tirapazamine; toremifene citrate; trestolone acetate; triciribine phosphate; 15 trimetrexate; trimetrexate glucuronate; triptorelin; tubulozole hydrochloride; uracil mustard; uredepa; vapreotide; verteporfin; vinblastine sulfate; vincristine sulfate; vindesine; vindesine sulfate; vinepidine sulfate; vinglycinate sulfate; vinleurosine sulfate; vinorelbine tartrate; vinrosidine sulfate; vinzolidine sulfate; vorozole; zeniplatin; zinostatin; zorubicin hydrochloride. Other anti-cancer drugs include, but are not limited to: 20-epi-1,25 20 dihydroxyvitamin D3; 5-ethynyluracil; abiraterone; aclarubicin; acylfulvene; adecyepol; adozelesin; aldesleukin; ALL-TK antagonists; altretamine; ambamustine; amidox; amifostine; aminolevulinic acid; amrubicin; amsacrine; anagrelide; anastrozole; andrographolide; angiogenesis inhibitors; antagonist D; antagonist G; antarelix; anti-dorsalizing morphogenetic protein-1; antiandrogen, prostatic carcinoma; antiestrogen; 25 antineoplaston; antisense oligonucleotides; aphidicolin glycinate; apoptosis gene modulators; apoptosis regulators; apurinic acid; ara-CDP-DL-PTBA; arginine deaminase; asulacrine; atamestane; atrimustine; axinastatin 1; axinastatin 2; axinastatin 3; azasetron; azatoxin; azatyrosine; baccatin III derivatives; balanol; batimastat; BCR/ABL antagonists; benzochlorins; benzoylstauroporine; beta lactam derivatives; beta-alethine; betaclamycin B; 30 betulinic acid; bFGF inhibitor; bicalutamide; bisantrene; bisaziridinylspermine; bisnafide; bistratene A; bizelesin; breflate; bropirimine; budotitane; buthionine sulfoximine; calcipotriol; calphostin C; camptothecin derivatives; canarypox IL-2; capecitabine; carboxamide-amino-triazole; carboxyamidotriazole; CaRest M3; CARN 700; cartilage derived inhibitor; carzelesin; casein kinase inhibitors (ICOS); castanospermine; cecropin B; 35 cetrorelix; chlorins; chloroquinoxaline sulfonamide; cicaprost; cis-porphyrin; cladribine;

clomifene analogues; clotrimazole; collismycin A; collismycin B; combretastatin A4; combretastatin analogue; conagenin; crambescidin 816; crisnatol; cryptophycin 8; cryptophycin A derivatives; curacin A; cyclopentanthraquinones; cycloplatam; cypemycin; cytarabine ocfosfate; cytolytic factor; cytostatin; dacliximab; decitabine; dehydrodideaminin B; deslorelin; dexamethasone; dexifosfamide; dexrazoxane; dexverapamil; diaziquone; didemnin B; didox; diethylnorspermine; dihydro-5-azacytidine; dihydrotaxol, 9-; dioxamycin; diphenyl spiromustine; docetaxel; docosanol; dolasetron; doxifluridine; droloxifene; dronabinol; duocarmycin SA; ebselen; ecomustine; edelfosine; edrecolomab; eflornithine; elemene; emitefur; epirubicin; epristeride; estramustine analogue; estrogen agonists; estrogen antagonists; etanidazole; etoposide phosphate; exemestane; fadrozole; fazarabine; fenretinide; filgrastim; finasteride; flavopiridol; flezelastine; fluasterone; fludarabine; fluorodaunorubicin hydrochloride; forfenimex; formestane; fostriecin; fotemustine; gadolinium texaphyrin; gallium nitrate; galocitabine; ganirelix; gelatinase inhibitors; gemcitabine; glutathione inhibitors; hepsulfam; heregulin; hexamethylene bisacetamide; hypericin; ibandronic acid; idarubicin; idoxifene; idramantone; ilmofosine; ilomastat; imidazoacridones; imiquimod; immunostimulant peptides; insulin-like growth factor-1 receptor inhibitor; interferon agonists; interferons; interleukins; iobenguane; iododoxorubicin; ipomeanol, 4- iroplact; irsogladine; isobengazole; isohomohalicondrin B; itasetron; jasplakinolide; kahalalide F; lamellarin-N triacetate; lanreotide; leinamycin; lenograstim; lentinan sulfate; leptolstatin; letrozole; leukemia inhibiting factor; leukocyte alpha interferon; leuprolide+estrogen+progesterone; leuprorelin; levamisole; liarozole; linear polyamine analogue; lipophilic disaccharide peptide; lipophilic platinum compounds; lissoclinamide 7; lobaplatin; lombricine; lometrexol; lonidamine; losoxantrone; lovastatin; loxoribine; lurtotecan; lutetium texaphyrin; lysofylline; lytic peptides; maitansine; 25 mannostatin A; marimastat; masoprolol; maspin; matrilysin inhibitors; matrix metalloproteinase inhibitors; menogaril; merbarone; meterelin; methioninase; metoclopramide; MIF inhibitor; mifepristone; miltefosine; mirimostim; mismatched double stranded RNA; mitoguazone; mitolactol; mitomycin analogues; mitonafide; mitotoxin fibroblast growth factor-saporin; mitoxantrone; mofarotene; molgramostim; monoclonal antibody, human chorionic gonadotrophin; monophosphoryl lipid A+myobacterium cell wall sk; mopidamol; multiple drug resistance gene inhibitor; multiple tumor suppressor 1-based therapy; mustard anticancer agent; mycaperoxide B; mycobacterial cell wall extract; myriaporone; N-acetyl-dinaline; N-substituted benzamides; nafarelin; nagrestip; naloxone+pentazocine; napavin; naphterpin; nartograstim; nedaplatin; nemorubicin; 30 neridronic acid; neutral endopeptidase; nilutamide; nisamycin; nitric oxide modulators;

nitroxide antioxidant; nitrullyn; O6-benzylguanine; octreotide; okicenone; oligonucleotides; onapristone; ondansetron; ondansetron; oracin; oral cytokine inducer; ormaplatin; osaterone; oxaliplatin; oxaunomycin; paclitaxel; paclitaxel analogues; paclitaxel derivatives; palauamine; palmitoylthizoxin; pamidronic acid; panaxytriol; panomifene; 5 parabactin; pazelliptine; pegaspargase; peldesine; pentosan polysulfate sodium; pentostatin; pentrozole; perflubron; perfosfamide; perillyl alcohol; phenazinomycin; phenylacetate; phosphatase inhibitors; picibanil; pilocarpine hydrochloride; pirarubicin; piritrexim; placetin A; placetin B; plasminogen activator inhibitor; platinum complex; platinum compounds; platinum-triamine complex; porfimer sodium; porfiromycin; prednisone; 10 propyl bis-acridone; prostaglandin J2; proteasome inhibitors; protein A-based immune modulator; protein kinase C inhibitor; protein kinase C inhibitors, microalgal; protein tyrosine phosphatase inhibitors; purine nucleoside phosphorylase inhibitors; purpurins; pyrazoloacridine; pyridoxylated hemoglobin polyoxyethylene conjugate; raf antagonists; raltitrexed; ramosetron; ras farnesyl protein transferase inhibitors; ras inhibitors; ras-GAP 15 inhibitor; retelliptine demethylated; rhenium Re 186 etidronate; rhizoxin; ribozymes; RII retinamide; rogletimide; rohitukine; romurtide; roquinimex; rubiginone B1; ruboxyl; safingol; saintopin; SarCNU; sarcophytol A; sargramostim; Sdi 1 mimetics; semustine; senescence derived inhibitor 1; sense oligonucleotides; signal transduction inhibitors; signal transduction modulators; single chain antigen binding protein; sizofiran; sobuzoxane; 20 sodium borocaptate; sodium phenylacetate; solverol; somatomedin binding protein; sonermin; sparfusic acid; spicamycin D; spiromustine; splenopentin; spongistatin 1; squalamine; stem cell inhibitor; stem-cell division inhibitors; stipiamide; stromelysin inhibitors; sulfinosine; superactive vasoactive intestinal peptide antagonist; suradista; suramin; swainsonine; synthetic glycosaminoglycans; tallimustine; tamoxifen methiodide; 25 tauromustine; tazarotene; tecogalan sodium; tegafur; tellurapyrylium; telomerase inhibitors; temoporfin; temozolomide; teniposide; tetrachlorodecaoxide; tetrazomine; thaliblastine; thiocoraline; thrombopoietin; thrombopoietin mimetic; thymalfasin; thymopoietin receptor agonist; thymotrinan; thyroid stimulating hormone; tin ethyl etiopurpurin; tirapazamine; titanocene bichloride; topsentin; toremifene; totipotent stem cell factor; translation 30 inhibitors; tretinoin; triacetyluridine; triciribine; trimetrexate; triptorelin; tropisetron; turosteride; tyrosine kinase inhibitors; typhostins; UBC inhibitors; ubenimex; urogenital sinus-derived growth inhibitory factor; urokinase receptor antagonists; vapreotide; variolin B; vector system, erythrocyte gene therapy; velaresol; veramine; verdins; verteporfin; vinorelbine; vinxaltine; vitaxin; vorozole; zanoterone; zeniplatin; zilascorb; and zinostatin 35 stimulamer.

The invention further encompasses a method of treating or preventing diseases or disorders ameliorated by the inhibition of PDE4 in a patient which comprise administering to a patient in need of such treatment or prevention a therapeutically effective amount of stereomerically pure Compound A, or a pharmaceutically acceptable prodrug, 5 metabolite, polymorph, salt, solvate, hydrate, or clathrate thereof. Disorders ameliorated by the inhibition of PDE4 include, but are not limited to, asthma, inflammation, chronic or acute obstructive pulmonary disease, chronic or acute pulmonary inflammatory disease, inflammatory bowel disease, Crohn's Disease, Bechet's Disease, colitis, ulcerative colitis, arthritis and inflammation due to reperfusion. In a preferred embodiment, the disease or 10 disorder to be treated or prevented is chronic obstructive pulmonary disease.

Specific methods of the invention can comprise the administration of an additional therapeutic agent such as, but not limited to, anti-inflammatory drugs, antihistamines and decongestants. Examples of such additional therapeutic agents include, but are not limited to: antihistamines including, but not limited to, ethanolamines, 15 ethylenediamines, piperazines, and phenothiazines; antinflammatory drugs; NSAIDS, including, but not limited to, salicylates, acetominophen, indomethacin, sulindac, etodolac, fenamates, tolmetin, ketorolac, diclofenac, ibuprofen, naproxen, fenoprofen, ketoprofen, flurbiprofen, oxaprozin, piroxicam, meloxicam, pyrazolon derivatives; and steriods including, but not limited to, cortical steroids and adrenocortical steroids.

20 Specific methods of the invention avoid or reduce drug-drug interactions and other adverse effects associated with agents used in the treatment of such disorders, including racemic substituted phenylethylsulfones.

The active compound of the invention (*i.e.*, Compound A) may be used in the treatment or prevention of a wide range of diseases and conditions. The magnitude of a 25 prophylactic or therapeutic dose of a particular active ingredient of the invention in the acute or chronic management of a disease or condition will vary, however, with the nature and severity of the disease or condition, and the route by which the active ingredient is administered. The dose, and perhaps the dose frequency, will also vary according to the age, body weight, and response of the individual patient. Suitable dosing regimens can be 30 readily selected by those skilled in the art with due consideration of such factors. In general, the recommended daily dose range for the conditions described herein lie within the range of from about 1 mg to about 1000 mg per day, given as a single once-a-day dose, preferably as divided doses throughout a day. More specifically, the daily dose is administered twice daily in equally divided doses. Specifically, a daily dose range should be from about 5 mg 35 to about 500 mg per day, more specifically, between about 10 mg and about 200 mg per

day. Specifically, the daily dose may be administered in 5 mg, 10 mg, 15 mg, 20 mg, 25 mg, 50 mg, or 100 mg dosage forms. In managing the patient, the therapy should be initiated at a lower dose, perhaps about 1 mg to about 25 mg, and increased if necessary up to about 200 mg to about 1000 mg per day as either a single dose or divided doses, 5 depending on the patient's global response. Alternatively, the daily dose is from 0.01 mg/kg to 100 mg/kg.

It may be necessary to use dosages of the active ingredient outside the ranges disclosed herein in some cases, as will be apparent to those of ordinary skill in the art. Furthermore, it is noted that the clinician or treating physician will know how and when to 10 interrupt, adjust, or terminate therapy in conjunction with individual patient response.

The phrases "therapeutically effective amount", "prophylactically effective amount" and "therapeutically or prophylactically effective amount," as used herein encompasses the above described dosage amounts and dose frequency schedules. Different therapeutically effective amounts may be applicable for different diseases and conditions, as 15 will be readily known by those of ordinary skill in the art. Similarly, amounts sufficient to treat or prevent such disorders, but insufficient to cause, or sufficient to reduce, adverse effects associated with conventional therapies are also encompassed by the above described dosage amounts and dose frequency schedules.

20 4.3. PHARMACEUTICAL COMPOSITIONS

Pharmaceutical compositions and single unit dosage forms comprising Compound A, or a pharmaceutically acceptable polymorph, prodrug, salt, solvate, hydrate, or clathrate thereof, are encompassed by the invention. Individual dosage forms of the invention may be suitable for oral, mucosal (including rectal, nasal, or vaginal), parenteral 25 (including subcutaneous, intramuscular, bolus injection, intraarterial, or intravenous), sublingual, transdermal, buccal, or topical administration.

Pharmaceutical compositions and dosage forms of the invention comprise stereomerically pure Compound A, or a pharmaceutically acceptable prodrug, metabolite, polymorph, salt, solvate, hydrate, or clathrate thereof. Pharmaceutical compositions and 30 dosage forms of the invention typically also comprise one or more pharmaceutically acceptable excipients.

A particular pharmaceutical composition encompassed by this embodiment comprises stereomerically pure Compound A, or a pharmaceutically acceptable polymorph, prodrug, salt, solvate, hydrate, or clathrate thereof, and at least one additional therapeutic 35 agent. Examples of additional therapeutic agents include, but are not limited to: anti-cancer

drugs and anti-inflammation therapies including, but not limited to, those listed above in section 4.2.

Single unit dosage forms of the invention are suitable for oral, mucosal (e.g., nasal, sublingual, vaginal, buccal, or rectal), parenteral (e.g., subcutaneous, intravenous, 5 bolus injection, intramuscular, or intraarterial), or transdermal administration to a patient. Examples of dosage forms include, but are not limited to: tablets; caplets; capsules, such as soft elastic gelatin capsules; cachets; troches; lozenges; dispersions; suppositories; ointments; cataplasms (poultices); pastes; powders; dressings; creams; plasters; solutions; patches; aerosols (e.g., nasal sprays or inhalers); gels; liquid dosage forms suitable for oral 10 or mucosal administration to a patient, including suspensions (e.g., aqueous or non-aqueous liquid suspensions, oil-in-water emulsions, or a water-in-oil liquid emulsions), solutions, and elixirs; liquid dosage forms suitable for parenteral administration to a patient; and sterile solids (e.g., crystalline or amorphous solids) that can be reconstituted to provide liquid dosage forms suitable for parenteral administration to a patient.

15 The composition, shape, and type of dosage forms of the invention will typically vary depending on their use. For example, a dosage form used in the acute treatment of inflammation or a related disorder may contain larger amounts of one or more of the active ingredients it comprises than a dosage form used in the chronic treatment of the same disease. Similarly, a parenteral dosage form may contain smaller amounts of one 20 or more of the active ingredients it comprises than an oral dosage form used to treat the same disease or disorder. These and other ways in which specific dosage forms encompassed by this invention will vary from one another will be readily apparent to those skilled in the art. *See, e.g., Remington's Pharmaceutical Sciences*, 18th ed., Mack Publishing, Easton PA (1990).

25 Typical pharmaceutical compositions and dosage forms comprise one or more excipients. Suitable excipients are well known to those skilled in the art of pharmacy, and non-limiting examples of suitable excipients are provided herein. Whether a particular excipient is suitable for incorporation into a pharmaceutical composition or dosage form depends on a variety of factors well known in the art including, but not limited to, the way 30 in which the dosage form will be administered to a patient. For example, oral dosage forms such as tablets may contain excipients not suited for use in parenteral dosage forms. The suitability of a particular excipient may also depend on the specific active ingredients in the dosage form.

35 Lactose-free compositions of the invention can comprise excipients that are well known in the art and are listed, for example, in the U.S. Pharmacopedia (USP) SP

(XXI)/NF (XVI). In general, lactose-free compositions comprise active ingredients, a binder/filler, and a lubricant in pharmaceutically compatible and pharmaceutically acceptable amounts. Preferred lactose-free dosage forms comprise active ingredients, microcrystalline cellulose, pre-gelatinized starch, and magnesium stearate.

5 This invention further encompasses anhydrous pharmaceutical compositions and dosage forms comprising active ingredients, since water can facilitate the degradation of some compounds. For example, the addition of water (e.g., 5%) is widely accepted in the pharmaceutical arts as a means of simulating long-term storage in order to determine characteristics such as shelf-life or the stability of formulations over time. *See, e.g.*, Jens T. 10 Carstensen, *Drug Stability: Principles & Practice*, 2d. Ed., Marcel Dekker, NY, NY, 1995, pp. 379-80. In effect, water and heat accelerate the decomposition of some compounds. Thus, the effect of water on a formulation can be of great significance since moisture and/or humidity are commonly encountered during manufacture, handling, packaging, storage, shipment, and use of formulations.

15 Anhydrous pharmaceutical compositions and dosage forms of the invention can be prepared using anhydrous or low moisture containing ingredients and low moisture or low humidity conditions. Pharmaceutical compositions and dosage forms that comprise lactose and at least one active ingredient that comprises a primary or secondary amine are preferably anhydrous if substantial contact with moisture and/or humidity during 20 manufacturing, packaging, and/or storage is expected.

25 An anhydrous pharmaceutical composition should be prepared and stored such that its anhydrous nature is maintained. Accordingly, anhydrous compositions are preferably packaged using materials known to prevent exposure to water such that they can be included in suitable formulary kits. Examples of suitable packaging include, but are not limited to, hermetically sealed foils, plastics, unit dose containers (e.g., vials), blister packs, and strip packs.

The invention further encompasses pharmaceutical compositions and dosage forms that comprise one or more compounds that reduce the rate by which an active 30 ingredient will decompose. Such compounds, which are referred to herein as "stabilizers," include, but are not limited to, antioxidants such as ascorbic acid, pH buffers, or salt buffers.

Like the amounts and types of excipients, the amounts and specific types of active ingredients in a dosage form may differ depending on factors such as, but not limited to, the route by which it is to be administered to patients. However, typical dosage forms of the invention comprise compound A, or a pharmaceutically acceptable salt, solvate, 35 clathrate, hydrate, polymorph or prodrug thereof lie within the range of from about 1 mg to

about 1000 mg per day, given as a single once-a-day dose in the morning but preferably as divided doses throughout the day taken with food. More specifically, the daily dose is administered twice daily in equally divided doses. Specifically, a daily dose range should be from about 5 mg to about 500 mg per day, more specifically, between about 10 mg and 5 about 200 mg per day. In managing the patient, the therapy should be initiated at a lower dose, perhaps about 1 mg to about 25 mg, and increased if necessary up to about 200 mg to about 1000 mg per day as either a single dose or divided doses, depending on the patient's global response.

10 **4.3.1. ORAL DOSAGE FORMS**

Pharmaceutical compositions of the invention that are suitable for oral administration can be presented as discrete dosage forms, such as, but are not limited to, tablets (e.g., chewable tablets), caplets, capsules, and liquids (e.g., flavored syrups). Such dosage forms contain predetermined amounts of active ingredients, and may be prepared by 15 methods of pharmacy well known to those skilled in the art. See generally, *Remington's Pharmaceutical Sciences*, 18th ed., Mack Publishing, Easton PA (1990).

Typical oral dosage forms of the invention are prepared by combining the active ingredient(s) in an intimate admixture with at least one excipient according to conventional pharmaceutical compounding techniques. Excipients can take a wide variety 20 of forms depending on the form of preparation desired for administration. For example, excipients suitable for use in oral liquid or aerosol dosage forms include, but are not limited to, water, glycols, oils, alcohols, flavoring agents, preservatives, and coloring agents. Examples of excipients suitable for use in solid oral dosage forms (e.g., powders, tablets, capsules, and caplets) include, but are not limited to, starches, sugars, micro-crystalline 25 cellulose, diluents, granulating agents, lubricants, binders, and disintegrating agents.

Because of their ease of administration, tablets and capsules represent the most advantageous oral dosage unit forms, in which case solid excipients are employed. If desired, tablets can be coated by standard aqueous or nonaqueous techniques. Such dosage forms can be prepared by any of the methods of pharmacy. In general, pharmaceutical 30 compositions and dosage forms are prepared by uniformly and intimately admixing the active ingredients with liquid carriers, finely divided solid carriers, or both, and then shaping the product into the desired presentation if necessary.

For example, a tablet can be prepared by compression or molding. Compressed tablets can be prepared by compressing in a suitable machine the active 35 ingredients in a free-flowing form such as powder or granules, optionally mixed with an

excipient. Molded tablets can be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent.

Examples of excipients that can be used in oral dosage forms of the invention include, but are not limited to, binders, fillers, disintegrants, and lubricants.

5 Binders suitable for use in pharmaceutical compositions and dosage forms include, but are not limited to, corn starch, potato starch, or other starches, gelatin, natural and synthetic gums such as acacia, sodium alginate, alginic acid, other alginates, powdered tragacanth, guar gum, cellulose and its derivatives (e.g., ethyl cellulose, cellulose acetate, carboxymethyl cellulose calcium, sodium carboxymethyl cellulose), polyvinyl pyrrolidone, 10 methyl cellulose, pre-gelatinized starch, hydroxypropyl methyl cellulose, (e.g., Nos. 2208, 2906, 2910), microcrystalline cellulose, and mixtures thereof.

Examples of fillers suitable for use in the pharmaceutical compositions and dosage forms disclosed herein include, but are not limited to, talc, calcium carbonate (e.g., granules or powder), microcrystalline cellulose, powdered cellulose, dextrates, kaolin, 15 mannitol, silicic acid, sorbitol, starch, pre-gelatinized starch, and mixtures thereof. The binder or filler in pharmaceutical compositions of the invention is typically present in from about 50 to about 99 weight percent of the pharmaceutical composition or dosage form.

Suitable forms of microcrystalline cellulose include, but are not limited to, the materials sold as AVICEL-PH-101, AVICEL-PH-103 AVICEL RC-581, 20 AVICEL-PH-105 (available from FMC Corporation, American Viscose Division, Avicel Sales, Marcus Hook, PA), and mixtures thereof. An specific binder is a mixture of microcrystalline cellulose and sodium carboxymethyl cellulose sold as AVICEL RC-581. Suitable anhydrous or low moisture excipients or additives include AVICEL-PH-103TM and Starch 1500 LM.

25 Disintegrants are used in the compositions of the invention to provide tablets that disintegrate when exposed to an aqueous environment. Tablets that contain too much disintegrant may disintegrate in storage, while those that contain too little may not disintegrate at a desired rate or under the desired conditions. Thus, a sufficient amount of disintegrant that is neither too much nor too little to detrimentally alter the release of the 30 active ingredients should be used to form solid oral dosage forms of the invention. The amount of disintegrant used varies based upon the type of formulation, and is readily discernible to those of ordinary skill in the art. Typical pharmaceutical compositions comprise from about 0.5 to about 15 weight percent of disintegrant, specifically from about 1 to about 5 weight percent of disintegrant.

Disintegrants that can be used in pharmaceutical compositions and dosage forms of the invention include, but are not limited to, agar-agar, alginic acid, calcium carbonate, microcrystalline cellulose, croscarmellose sodium, crospovidone, polacrilin potassium, sodium starch glycolate, potato or tapioca starch, pre-gelatinized starch, other starches, clays, other alginic acids, other celluloses, gums, and mixtures thereof.

5 Lubricants that can be used in pharmaceutical compositions and dosage forms of the invention include, but are not limited to, calcium stearate, magnesium stearate, mineral oil, light mineral oil, glycerin, sorbitol, mannitol, polyethylene glycol, other glycols, stearic acid, sodium lauryl sulfate, talc, hydrogenated vegetable oil (e.g., peanut oil, 10 cottonseed oil, sunflower oil, sesame oil, olive oil, corn oil, and soybean oil), zinc stearate, ethyl oleate, ethyl laurate, agar, and mixtures thereof. Additional lubricants include, for example, a syloid silica gel (AEROSIL 200, manufactured by W.R. Grace Co. of Baltimore, MD), a coagulated aerosol of synthetic silica (marketed by Degussa Co. of Plano, TX), CAB-O-SIL (a pyrogenic silicon dioxide product sold by Cabot Co. of Boston, MA), and 15 mixtures thereof. If used at all, lubricants are typically used in an amount of less than about 1 weight percent of the pharmaceutical compositions or dosage forms into which they are incorporated.

4.3.2. DELAYED RELEASE DOSAGE FORMS

20 Active ingredients of the invention can be administered by controlled release means or by delivery devices that are well known to those of ordinary skill in the art. Examples include, but are not limited to, those described in U.S. Patent Nos.: 3,845,770; 3,916,899; 3,536,809; 3,598,123; and 4,008,719, 5,674,533, 5,059,595, 5,591,767, 5,120,548, 5,073,543, 5,639,476, 5,354,556, and 5,733,566, each of which is incorporated 25 herein by reference. Such dosage forms can be used to provide slow or controlled-release of one or more active ingredients using, for example, hydropropylmethyl cellulose, other polymer matrices, gels, permeable membranes, osmotic systems, multilayer coatings, microparticles, liposomes, microspheres, or a combination thereof to provide the desired release profile in varying proportions. Suitable controlled-release formulations known to 30 those of ordinary skill in the art, including those described herein, can be readily selected for use with the active ingredients of the invention. The invention thus encompasses single unit dosage forms suitable for oral administration such as, but not limited to, tablets, capsules, gelcaps, and caplets that are adapted for controlled-release.

35 All controlled-release pharmaceutical products have a common goal of improving drug therapy over that achieved by their non-controlled counterparts. Ideally, the

use of an optimally designed controlled-release preparation in medical treatment is characterized by a minimum of drug substance being employed to cure or control the condition in a minimum amount of time. Advantages of controlled-release formulations include extended activity of the drug, reduced dosage frequency, and increased patient 5 compliance. In addition, controlled-release formulations can be used to affect the time of onset of action or other characteristics, such as blood levels of the drug, and can thus affect the occurrence of side (e.g., adverse) effects.

Most controlled-release formulations are designed to initially release an amount of drug (active ingredient) that promptly produces the desired therapeutic effect, and 10 gradually and continually release of other amounts of drug to maintain this level of therapeutic or prophylactic effect over an extended period of time. In order to maintain this constant level of drug in the body, the drug must be released from the dosage form at a rate that will replace the amount of drug being metabolized and excreted from the body. Controlled-release of an active ingredient can be stimulated by various conditions including, 15 but not limited to, pH, temperature, enzymes, water, or other physiological conditions or compounds.

4.3.3. PARENTERAL DOSAGE FORMS

Parenteral dosage forms can be administered to patients by various routes 20 including, but not limited to, subcutaneous, intravenous (including bolus injection), intramuscular, and intraarterial. Because their administration typically bypasses patients' natural defenses against contaminants, parenteral dosage forms are preferably sterile or capable of being sterilized prior to administration to a patient. Examples of parenteral dosage forms include, but are not limited to, solutions ready for injection, dry products 25 ready to be dissolved or suspended in a pharmaceutically acceptable vehicle for injection, suspensions ready for injection, and emulsions.

Suitable vehicles that can be used to provide parenteral dosage forms of the invention are well known to those skilled in the art. Examples include, but are not limited to: Water for Injection USP; aqueous vehicles such as, but not limited to, Sodium Chloride 30 Injection, Ringer's Injection, Dextrose Injection, Dextrose and Sodium Chloride Injection, and Lactated Ringer's Injection; water-miscible vehicles such as, but not limited to, ethyl alcohol, polyethylene glycol, and polypropylene glycol; and non-aqueous vehicles such as, but not limited to, corn oil, cottonseed oil, peanut oil, sesame oil, ethyl oleate, isopropyl myristate, and benzyl benzoate.

Compounds that increase the solubility of one or more of the active ingredients disclosed herein can also be incorporated into the parenteral dosage forms of the invention.

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4.3.4. TRANSDERMAL, TOPICAL, AND MUCOSAL DOSAGE FORMS

Transdermal, topical, and mucosal dosage forms of the invention include, but are not limited to, ophthalmic solutions, sprays, aerosols, creams, lotions, ointments, gels, 10 solutions, emulsions, suspensions, or other forms known to one of skill in the art. *See, e.g., Remington's Pharmaceutical Sciences*, 16th and 18th eds., Mack Publishing, Easton PA (1980 & 1990); and *Introduction to Pharmaceutical Dosage Forms*, 4th ed., Lea & Febiger, Philadelphia (1985). Dosage forms suitable for treating mucosal tissues within the oral 15 cavity can be formulated as mouthwashes or as oral gels. Further, transdermal dosage forms include "reservoir type" or "matrix type" patches, which can be applied to the skin and worn for a specific period of time to permit the penetration of a desired amount of active ingredients.

Suitable excipients (*e.g.*, carriers and diluents) and other materials that can be used to provide transdermal, topical, and mucosal dosage forms encompassed by this 20 invention are well known to those skilled in the pharmaceutical arts, and depend on the particular tissue to which a given pharmaceutical composition or dosage form will be applied. With that fact in mind, typical excipients include, but are not limited to, water, acetone, ethanol, ethylene glycol, propylene glycol, butane-1,3-diol, isopropyl myristate, isopropyl palmitate, mineral oil, and mixtures thereof to form lotions, tinctures, creams, 25 emulsions, gels or ointments, which are non-toxic and pharmaceutically acceptable. Moisturizers or humectants can also be added to pharmaceutical compositions and dosage forms if desired. Examples of such additional ingredients are well known in the art. *See, e.g., Remington's Pharmaceutical Sciences*, 16th and 18th eds., Mack Publishing, Easton PA (1980 & 1990).

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Depending on the specific tissue to be treated, additional components may be used prior to, in conjunction with, or subsequent to treatment with active ingredients of the invention. For example, penetration enhancers can be used to assist in delivering the active ingredients to the tissue. Suitable penetration enhancers include, but are not limited to: acetone; various alcohols such as ethanol, oleyl, and tetrahydrofuryl; alkyl sulfoxides such 35 as dimethyl sulfoxide; dimethyl acetamide; dimethyl formamide; polyethylene glycol; pyrrolidones such as polyvinylpyrrolidone; Kollidon grades (Povidone, Polyvidone); urea;

and various water-soluble or insoluble sugar esters such as Tween 80 (polysorbate 80) and Span 60 (sorbitan monostearate).

The pH of a pharmaceutical composition or dosage form, or of the tissue to which the pharmaceutical composition or dosage form is applied, may also be adjusted to improve delivery of one or more active ingredients. Similarly, the polarity of a solvent carrier, its ionic strength, or tonicity can be adjusted to improve delivery. Compounds such as stearates can also be added to pharmaceutical compositions or dosage forms to advantageously alter the hydrophilicity or lipophilicity of one or more active ingredients so as to improve delivery. In this regard, stearates can serve as a lipid vehicle for the formulation, as an emulsifying agent or surfactant, and as a delivery-enhancing or penetration-enhancing agent. Different salts, hydrates or solvates of the active ingredients can be used to further adjust the properties of the resulting composition.

4.3.5. KITS

Typically, active ingredients of the invention are preferably not administered to a patient at the same time or by the same route of administration. This invention therefore encompasses kits which, when used by the medical practitioner, can simplify the administration of appropriate amounts of active ingredients to a patient.

A typical kit of the invention comprises a unit dosage form of compound A, or a pharmaceutically acceptable salt, solvate, hydrate, clathrate, polymorph or prodrug thereof, and a unit dosage form of a second active ingredient. Examples of second active ingredients include, but are not limited to, those listed in section 4.2 above.

Kits of the invention can further comprise devices that are used to administer the active ingredient(s). Examples of such devices include, but are not limited to, syringes, drip bags, patches, and inhalers.

Kits of the invention can further comprise pharmaceutically acceptable vehicles that can be used to administer one or more active ingredients. For example, if an active ingredient is provided in a solid form that must be reconstituted for parenteral administration, the kit can comprise a sealed container of a suitable vehicle in which the active ingredient can be dissolved to form a particulate-free sterile solution that is suitable for parenteral administration. Examples of pharmaceutically acceptable vehicles include, but are not limited to: Water for Injection USP; aqueous vehicles such as, but not limited to, Sodium Chloride Injection, Ringer's Injection, Dextrose Injection, Dextrose and Sodium Chloride Injection, and Lactated Ringer's Injection; water-miscible vehicles such as, but not limited to, ethyl alcohol, polyethylene glycol, and polypropylene glycol; and non-aqueous

vehicles such as, but not limited to, corn oil, cottonseed oil, peanut oil, sesame oil, ethyl oleate, isopropyl myristate, and benzyl benzoate.

5. EXAMPLES

5.1. EXAMPLE 1: SYNTHESIS OF 2-[1-(3-ETHOXY-4-METHOXYPHENYL)-2-METHYLSULFONYLETHYL]-4-ACETYLAMINOISOINDOLINE-1,3-DIONE

A stirred solution of 1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethylamine (1.0g, 3.7 mmol) and 3 -acetamidophthalic anhydride (751 mg, 3.66 mmol) in acetic acid (20 mL) was heated at reflux for 15 h. The solvent was removed in vacuo to yield an oil. Chromatography of the resulting oil yielded the product as a yellow solid (1.0 g, 59% yield): mp, 144°C.; ¹H NMR (CDCl₃) δ1.47 (t, J=7.0 Hz, 3H, CH₃), 2.26 (s, 3H, CH₃), 2.88 (s, 3H, CH₃), 3.75 (dd, J=4.4, 14.3 Hz, 1H, CHH), 3.85 (s, 3H, CH₃), 4.11 (q, J= 7Hz, 2H, CH₂), 5.87 (dd, J=4.3, 10.5 Hz, 1H, NCH), 6.82-6.86 (m, 1H, Ar), 7.09-7.11 (m, 2H, Ar), 7.47 (d, J=7 Hz, 1H, Ar), 7.64 (t, J= 8Hz, 1H, Ar), 8.74 (d, J= 8 Hz, 1H, Ar), 9.49 (br s, 1H, NH); ¹³C NMR (CDCl₃) δ14.61, 24.85, 41.54, 48.44, 54.34, 55.85, 64.43, 111.37, 112.34, 115.04, 118.11, 120.21, 124.85, 129.17, 130.96, 136.01, 137.52, 148.54, 149.65, 167.38, 169.09, 169.40; Anal Calc'd. for C₂₂H₂₄NO₇S: C, 57.38; H, 5.25; N, 6.08. Found: C, 57.31; H, 5.34; N, 5.83.

25 5.2. EXAMPLE 2: SYNTHESIS OF 2-[1-(3-ETHOXY-4-METHOXYPHENYL)-2-METHYLSULFONYLETHYL]-4-ACETYLAMINOISOINDOLINE-1,3-DIONE

Preparation of 3-aminophthalic acid

10% Pd/C (2.5 g), 3-nitrophthalic acid (75.0 g, 355 mmol) and ethanol (1.5 L) were charged to a 2.5 L Parr hydrogenator, under a nitrogen atmosphere. Hydrogen was charged to the reaction vessel for up to 55 psi. The mixture was shaken for 13 hours, maintaining hydrogen pressure between 50 and 55 psi. Hydrogen was released and the mixture was purged with nitrogen 3 times. The suspension was filtered through a celite bed and rinsed with methanol. The filtrate was concentrated *in vacua*. The resulting solid was reslurried in ether and isolated by vacuum filtration. The solid was dried *in vacua* to a constant weight, affording 54 g (84% yield) of 3-aminophthalic acid as a yellow product. ¹H-NMR (DMSO-d6) δ: 3.17 (s, 2H), 6.67 (d, 1H), 6.82 (d, 1H), 7.17 (t, 1H), 8-10 (brs, 2H). ¹³C-NMR(DMSO-d6)δ: 112.00, 115.32, 118.20, 131.28, 135.86, 148.82, 169.15, 170.09.

Preparation of 3-acetamidophthalic anhydride

A 1 L 3-necked round bottom flask was equipped with a mechanical stirrer, thermometer, and condenser and charged with 3-aminophthalic acid (108 g, 596 mmol) and acetic anhydride (550 mL). The reaction mixture was heated to reflux for 3 hours and 5 cooled to ambient temperature and further to 0-5 °C for another 1 hour. The crystalline solid was collected by vacuum filtration and washed with ether. The solid product was dried *in vacuo* at ambient temperature to a constant weight, giving 75 g (61% yield) of 3-acetamidophthalic anhydride as a white product. ¹H-NMR (CDCl₃) δ: 2.21 (s, 3H), 7.76 (d, 1H), 7.94 (t, 1H), 8.42 (d, 1H), 9.84 (s, 1H).

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Generation of (R)-2-(3-ethoxy-4-methoxyphenyl)-1-(methylsulphonyl)-eth-2-ylamine -acetyl-D-leucine salt

A 500 mL 3-necked Round Bottom Flask equipped with a mechanical stirrer, thermometer, and condenser was charged with 2-(3-ethoxy-4-methoxyphenyl)-1-(methylsulphonyl)-eth-2-ylamine (26.1 g, 95.5 mmol), N-acetyl-D-leucine (14.9 g, 86.0 mmol), and methanol (215 mL). The stirred slurry was heated to reflux for 1 hour. The stirred mixture was allowed to cool to ambient temperature and stirring was continued for another 3 hours at ambient temperature. The slurry was filtered and the filter cake was 20 washed with methanol (130 mL). The solid was air-dried and then dried *in vacuo* at 30 °C to a constant weight, giving 36.0 g (94% yield based on N-acetyl-D-leu) of (R)-2-(3-ethoxy-4-methoxyphenyl)-1-(methylsulphonyl)-eth-2-ylamine -N-acetyl-D-leucine salt (97.6% ee). Chiral HPLC (1/99 EtOH/20 mM KH₂PO₄ @pH 7.0, Ultron Chiral ES-OVS from Agilent Technologies, 150 mm x 4.6 mm, 0.5 mL/min., @240 nm): 13.0 min (S-isomer, 1.2%), 14.5 min (R-isomer, 98.8%).

Preparation of Compound A

A 500 mL 3-necked Round Bottom Flask equipped with a mechanical stirrer, thermometer, and condenser was charged with (R)-2-(3-ethoxy-4-methoxyphenyl)-1-(methylsulphonyl)-eth-2-ylamine-N-acetyl-D-leucine salt (20 g, 44.8 mmol), 3-acetamidophthalic anhydride (9.6 g, 47.0 mmol), and glacial acetic acid. The mixture was refluxed over night and then cooled to <50 °C. The solvent was removed *in vacuo*, and the residue was dissolved in ethyl acetate. The resulting solution was washed with water (250 mL x 2), saturated aq NaHCO₃ (250 mL x 2), brine (250 mL x 2), and dried over sodium sulphate. The solvent was removed *in vacuo* and the residue recrystallized from ethanol 35

(150 mL). The solid was isolated by vacuum filtration and washed with ethanol (90 mL x 2). The product was dried *in vacuo* at 30 °C to a constant weight, affording 17.5 g (85% yield) of Compound A (98% ee). Chiral HPLC (15/85 EtOH/20 mM KH₂PO₄ @pH 3.5, Ultron Chiral ES-OVS from Agilent Technologies, 150 mm x 4.6 mm, 0.4 mL/min., @240 nm): 20.5 min (*S*-isomer, 1.0%). 23.2 min (*R*-isomer, 99.0%). ¹H-NMR (CDCl₃) δ: 1.47 (t, 3H), 2.26 (s, 3H), 2.87 (s, 3H), 3.68-3.76 (dd, 1H), 3.85 (s, 3H), 4.07-4.15 (q, 2H), 4.51-4.60 (dd, 1H), 5.84-5.90 (dd, 1H), 6.82-8.77 (m, 6H), 9.46 (s, 1H) ppm. ¹³C-NMR (DMSO-d₆) δ: 14.69, 24.95, 41.65, 48.58, 54.52, 55.95, 64.54, 111.48, 112.43, 115.13, 118.24, 120.31, 124.98, 129.25, 131.05, 136.13, 137.64, 148.66, 149.78, 167.50, 169.16, 169.52 ppm.

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5.3. EXAMPLE 3: TNF-α INHIBITION

Mouse LPS-induced serum TNF-α inhibition

Compounds were tested in this animal model according to previously 15 described methods (Corral et al. 1996, *Mol. Med* 2:506-515). Mouse LPS-induced serum TNF-α inhibition (ED₅₀, mg/kg, p.o.) >1.

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LPS-induced TNF-α production

Lipopolysaccharide (LPS) is an endotoxin produced by gram-negative bacteria such as *E. coli* which induces production of many pro-inflammatory cytokines, including TNF-α. In peripheral blood mononuclear cells (PBMC), the TNF-α produced in response to LPS is derived from monocytes, which comprise approximately 5-20% of the total PBMC. Compounds were tested for the ability to inhibit LPS-induced TNF-α production from human PBMC as previously described (Muller et al. 1996, *J. Med Chem.* 39:3238). PBMC from normal donors were obtained by Ficoll Hypaque (Pharmacia, Piscataway, NJ, USA) density centrifugation. Cells were cultured in RPMI (Life Technologies, Grand Island, NY, USA) supplemented with 10% AB± human serum (Gemini Bio-products, Woodland, CA, USA), 2 mM L-glutamine, 100 U/ml penicillin, and 100 µg/ml streptomycin (Life Technologies).

25

PBMC (2 x 10⁵ cells) were plated in 96-well flat-bottom Costar tissue culture plates (Corning, NY, USA) in triplicate. Cells were stimulated with LPS (Sigma, St. Louis, MO, USA) at 100 ng/ml in the absence or presence of compounds. Compounds (Celgene Corp., Warren, NJ, USA) were dissolved in DMSO (Sigma) and further dilutions were done in culture medium immediately before use. The final DMSO concentration in all samples 30 was 0.25%. Compounds were added to cells 1 hour before LPS stimulation. Cells were

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incubated for 18-20 hours at 37°C in 5% CO₂ and supernatants were then collected, diluted with culture medium and assayed for TNF- α levels by ELISA (Endogen, Boston, MA, USA). LPS-induced TNF- α IC₅₀ = 371 nM.

5 *IL-1 β -induced TNF- α production*

During the course of inflammatory diseases, TNF- α production is often stimulated by the cytokine IL-1 β , rather than by bacterially derived LPS. Compounds were tested for the ability to inhibit IL-1 β -induced TNF- α production from human PBMC as described above for LPS-induced TNF- α production, except that the PBMC were isolated 10 from source leukocyte units (Sera-Tec Biologicals, North Brunswick, NJ, USA) by centrifugation on Ficoll-Paque Plus (Amersham Pharmacia, Piscataway, NJ, USA), plated in 96-well tissue culture plates at 3 x 10⁵ cells/well in RPMI-1640 medium (BioWhittaker, Walkersville, Maryland, USA) containing 10% heat-inactivated fetal bovine serum (Hyclone), 2 mM L-glutamine, 100 U/ml penicillin, and 100 mg/ml streptomycin (complete 15 medium), pretreated with compounds at 10, 2, 0.4, 0.08, 0.016, 0.0032, 0.00064, and 0 μ M in duplicate at a final DMSO concentration of 0.1% at 37°C in a humidified incubator at 5% CO₂ for 1 hour, then stimulated with 50 ng/ml recombinant human IL-1 β (Endogen) for 18 hours.

20 **5.4. EXAMPLE 4: PDE SELECTIVITY**

PDE1, 2, 3, 5, and 6 enzyme assays

The specificity of compounds for PDE4 was assessed by testing at a single concentration (10 μ M) against bovine PDE1, human PDE2, PDE3, and PDE5 from human platelets (Hidaka and Asano 1976, *Biochem. Biophys. Acta* 429:485, and Nicholsen et al. 25 1991, *Trends Pharmacol. Sci.* 12:19), and PDE6 from bovine retinal rod outer segments (Baehr et al. 1979, *J. Biol. Chem.* 254:11669, and Gillespie et al. 1989, *Mol. Pharm.* 36:773).

PDE7 enzyme assay

30 PDE7 is a cAMP-selective PDE expressed mainly in T cells and in skeletal muscle. T cell-derived cytokines such as IL-2 and IFN- γ are potentially regulatable via PDE7 inhibition. PDE7 was purified from Hut78 human T cells by anion exchange chromatography as previously described (Bloom and Beavo 1996, *Proc. Natl. Acad. Sci. USA* 93:14188-14192). Compounds were tested against the PDE7 preparation in the presence of 10 nM cAMP as described for PDE4 below.

Table 1.

| | Racemic Compound | Compound B* | Compound A |
|---|------------------|-------------|------------|
| PDE Inhibition | | | |
| PDE4 IC ₅₀ (from U937 cells) (nM) | 81.8 | 73.5 | 611 |
| PDE1 (% inhib at 10 μ M) | 9% | 23% | 27% |
| PDE2 (% inhib at 10 μ M) | 19% | 6% | 10% |
| PDE3 (% inhib at 10 μ M) | 21% | 20% | 31% |
| PDE5 (% inhib at 10 μ M) | 3% | 3% | -9% |
| PDE6 (% inhib at 10 μ M) | ND | -6% | 10% |
| PDE7 IC ₅₀ (nM) | 22110 | 20500 | ND |
| PDE Specificity Ratios from above data (*fold) | | | |
| PDE4/PDE1 | >2700 | >500 | >50 |
| PDE4/PDE2 | >800 | >10000 | >260 |
| PDE4/PDE3 | >670 | >1200 | >45 |
| PDE4/PDE5 | >12000 | >30000 | >39000 |
| PDE4/PDE6 | ND | >40000 | >250 |
| PDE7 IC ₅₀ /PDE4 IC ₅₀ | 270 | 279 | ND |

*Compound B is the opposite enantiomer of Compound A.

5.5. EXAMPLE 5: PDE4 INHIBITION

PDE4 (U937 cell-derived) enzyme assay

PDE4 enzyme was purified from U937 human monocytic cells by gel filtration chromatography as previously described (Muller et al. 1998, *Bioorg. & Med Chem Lett* 8:2669-2674). Phosphodiesterase reactions were carried out in 50 mM Tris HCl pH 7.5, 5 mM MgCl₂, 1 μ M cAMP, 10 nM [³H]-cAMP for 30 min at 30°C, terminated by boiling, treated with 1 mg/ml snake venom, and separated using AG-IXS ion exchange resin (BioRad) as described (Muller et al. 1998, *Bioorg. & Med Chem Lett* 8:2669-2674). Reactions consumed less than 15% of available substrate.

5.6. EXAMPLE 6: AQUEOUS SOLUBILITY

Equilibrium solubilities were measured in pH 7.4 aqueous buffer. The pH 7.4 buffer was prepared by adjusting the pH of a 0.07 M NaH₂PO₄ solution to 7.4 with 10 N NaOH. The ionic strength of the solution was 0.15. At least 1 mg of powder was combined with 1

ml of buffer to make >1 mg/ml mixture. These samples were shaken for >2 hours and left to stand overnight at room temperature. The samples were then filtered through a 0.45- μ m Nylon syringe filter that was first saturated with the sample. The filtrate was sampled twice, consecutively. The filtrate was assayed by HPLC against standards prepared in 50% 5 methanol. Compound A has 3.5-fold greater aqueous solubility than the racemic mixture. Measured solubility Compound A = 0.014 mg/mL; racemic mixture = 0.0034mg/mL.

5.7. EXAMPLE 7: 200 MG DOSAGE CAPSULE

Table III illustrates a batch formulation and single dosage formulation for a 200 mg 10 Compound A single dose unit, i.e., about 40 percent by weight, in a size #0 capsule.

Table III. Formulation for 200 mg capsule

| Material | Percent By Weight | Quantity (mg/tablet) | Quantity (kg/batch) |
|---------------------------------|-------------------|----------------------|---------------------|
| Compound A | 40.0% | 200 mg | 16.80 kg |
| Pregelatinized Corn Starch, NF5 | 9.5% | 297.5 mg | 24.99 kg |
| Magnesium Stearate | 0.5% | 2.5 mg | 0.21 kg |
| Total | 100.0% | 500 mg | 42.00 kg |

20

The pregelatinized corn starch (SPRESS B-820) and Compound A components are passed through a 710 μ m screen and then are loaded into a Diffusion Mixer with a baffle insert and blended for 15 minutes. The magnesium stearate is passed through a 210 μ m screen and is added to the Diffusion Mixer. The blend is then encapsulated in a size #0 25 capsule, 500 mg per capsule (8400 capsule batch size) using a Dosator type capsule filling machine.

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5.8. EXAMPLE 8: 100 MG ORAL DOSAGE FORM

Table IV illustrates a batch formulation and a single dose unit formulation containing 100 mg of Compound A.

Table IV. Formulation for 100 mg tablet

| | Material | Percent by Weight | Quantity (mg/tablet) | Quantity (kg/batch) |
|----|----------------------------------|-------------------|----------------------|---------------------|
| 5 | Compound A | 40% | 100.00 | 20.00 |
| 10 | Microcrystalline Cellulose, NF | 53.5% | 133.75 | 26.75 |
| 15 | Pluronic F-68 Surfactant | 4.0% | 10.00 | 2.00 |
| | Croscarmellose Sodium Type A, NF | 2.0% | 5.00 | 1.00 |
| | Magnesium Stearate, NF | 0.5% | 1.25 | 0.25 |
| | Total | 100.0% | 250.00 mg | 50.00 kg |

The microcrystalline cellulose, croscarmellose sodium, and Compound A components are passed through a #30 mesh screen (about 430 μ to about 655 μ). The Pluronic F-68® (manufactured by JRH Biosciences, Inc. of Lenexa, KS) surfactant is passed through a #20 mesh screen (about 457 μ to about 1041 μ). The Pluronic F-68® surfactant and 0.5 kgs of croscarmellose sodium are loaded into a 16 qt. twin shell tumble blender and are mixed for about 5 minutes. The mix is then transferred to a 3 cubic foot twin shell tumble blender where the microcrystalline cellulose is added and blended for about 5 minutes. The thalidomide is added and blended for an additional 25 minutes. This pre-blend is passed through a roller compactor with a hammer mill attached at the discharge of the roller compactor and moved back to the tumble blender. The remaining croscarmellose sodium and magnesium stearate is added to the tumble blender and blended for about 3 minutes. The final mixture is compressed on a rotary tablet press with 250 mg per tablet (200,000 tablet batch size).

5.9. EXAMPLE 9: AEROSOL DOSAGE FORM

A concentrate is prepared by combining Compound A, and a 12.6 kg portion of the trichloromonofluoromethane in a sealed stainless steel vessel equipped with a high shear mixer. Mixing is carried out for about 20 minutes. The bulk suspension is then

5 prepared in the sealed vessel by combining the concentrate with the balance of the propellants in a bulk product tank that is temperature controlled to 21° to 27 °C. and pressure controlled to 2.8 to 4.0 BAR. 17 ml aerosol containers which have a metered valve which is designed to provide 100 inhalations of the composition of the invention. Each container is provided with the following:

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| | |
|----------------------------------|-----------------|
| Compound A | 0.0120 g |
| trichloromonofluoromethane | 1.6939 g |
| dichlorodifluoromethane | 3.7175g |
| <u>dichlorotetrafluoroethane</u> | <u>1.5766 g</u> |
| 15 total | 7.0000 g |

While the invention has been described with respect to the particular embodiments, it will be apparent to those skilled in the art that various changes and modifications may be made without departing from the spirit and scope of the invention as defined in the claims.

20 Such modifications are also intended to fall within the scope of the appended claims.

THE CLAIMS

What is claimed is:

- 5 1. A method of inhibiting TNF- α production which comprises contacting a cell which produces TNF- α with an effective amount of stereomerically pure (-)-2-[1-(3-Ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione, or a pharmaceutically acceptable prodrug, metabolite, polymorph, salt, solvate, hydrate, or clathrate thereof.
- 10 2. A method of inhibiting PDE4 activity which comprises contacting PDE4 with an effective amount of stereomerically pure (-)-2-[1-(3-Ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione, or a pharmaceutically acceptable prodrug, metabolite, polymorph, salt, solvate, hydrate, or clathrate thereof.
- 15 3. The method of claim 1 or 2 wherein the contact is in a mammalian cell.
- 20 4. The method of claim 3 wherein the cell is human.
- 25 5. A method of treating or preventing diseases or disorders ameliorated by reduction of levels of TNF- α in a patient which comprises administering to a patient in need of such treatment or prevention a therapeutically or prophylactically effective amount of stereomerically pure (-)-2-[1-(3-Ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione, or a pharmaceutically acceptable prodrug, metabolite, polymorph, salt, solvate, hydrate, or clathrate thereof.
- 30 6. A method of treating or preventing cancer which comprises administering to a patient in need of such treatment or prevention a therapeutically or prophylactically effective amount of stereomerically pure (-)-2-[1-(3-Ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione, or a pharmaceutically acceptable prodrug, metabolite, polymorph, salt, solvate, hydrate, or clathrate thereof.

7. The method of claim 5 or 6 further comprising administering to a patient in need of such treatment or prevention a therapeutically or prophylactically effective amount of an alkylating agent, nitrogen mustard, a JNK inhibitor, antibiotic, antineoplastic agent, ethylenimine, methylmelamine alkyl sulfonate, nitrosourea, triazene, 5 folic acid analog, pyrimidine analog, purine analog, vinca alkaloid, epipodophyllotoxin, a topoisomerase inhibitor, or an anti-cancer vaccine.

8. The method of claim 6 wherein the cancer is a solid tumor.

10 9. The method of claims 6 wherein the cancer is a blood borne tumor.

15 10. The method of claim 6 wherein the cancer is multiple myeloma, acute leukemia, lymphoblastic leukemia, myelogenous leukemia, lymphocytic leukemia, or myelocytic leukemia.

11. The method of claim 8 wherein the solid tumor is a tumor of the breast, colon, rectum, colorectum, kidney, or a glioma.

20 12. The method of claim 5 or 6 wherein the patient is a mammal.

13. The method of claim 5 or 6 wherein the stereomerically pure (-)-2-[1-(3-Ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione is administered parenterally, transdermally, mucosally, nasally, buccally, sublingually, or orally.

25 14. The method of claim 13 wherein the stereomerically pure (-)-2-[1-(3-Ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione is administered orally.

30 15. The method of claim 14 wherein the stereomerically pure (-)-2-[1-(3-Ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione is administered orally in a tablet or capsule form.

35 16. The method of claim 15 wherein the therapeutically or prophylactically effective amount is from about 1 mg to about 1000 mg per day.

17. The method of claim 16 wherein the therapeutically or prophylactively effective amount is from about 5 mg to about 500 mg per day.

18. The method of claim 17 wherein the therapeutically or prophylactively effective amount is from about 10 mg to about 200 mg per day.

19. A method of treating or preventing diseases or disorders ameliorated by the inhibition of PDE4 in a patient which comprises administering to a patient in need of such treatment or prevention a therapeutically or prophylactically effective amount of stereomerically pure (-)-2-[1-(3-Ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione, or a pharmaceutically acceptable prodrug, metabolite, polymorph, salt, solvate, hydrate, or clathrate thereof.

20. A method of treating or preventing depression, asthma, inflammation, inflammatory skin disease, psoriasis, atopic dermatitis, contact dermatitis, rheumatoid arthritis, osteoarthritis, chronic obstructive pulmonary disease, chronic pulmonary inflammatory disease, inflammatory bowel disease, Crohn's Disease, Bechet's Disease or colitis which comprises administering to a patient in need of such treatment or prevention a therapeutically or prophylactically effective amount of stereomerically pure (-)-2-[1-(3-Ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione, or a pharmaceutically acceptable prodrug, metabolite, polymorph, salt, solvate, hydrate, or clathrate thereof.

21. A method of controlling cAMP levels in a cell which comprises contacting a cell with an effective amount of stereomerically pure (-)-2-[1-(3-Ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione, or a pharmaceutically acceptable prodrug, metabolite, polymorph, salt, solvate, hydrate, or clathrate thereof.

22. A method of treating or preventing MDS in a patient which comprises administering to a patient in need of such treatment or prevention a therapeutically or prophylactically effective amount of stereomerically pure (-)-2-[1-(3-Ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione, or a pharmaceutically acceptable prodrug, metabolite, polymorph, salt, solvate, hydrate, or clathrate thereof.

23. A method of treating or preventing MPD in a patient which comprises administering to a patient in need of such treatment or prevention a therapeutically or prophylactically effective amount of stereomerically pure (-)-2-[1-(3-Ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminooindoline-1,3-dione, or a pharmaceutically acceptable prodrug, metabolite, polymorph, salt, solvate, hydrate, or clathrate thereof.

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24. A method of treating or preventing complex regional pain syndrome in a patient which comprises administering to a patient in need of such treatment or prevention a therapeutically or prophylactically effective amount of stereomerically pure (-)-2-[1-(3-Ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminooindoline-1,3-dione, or a pharmaceutically acceptable prodrug, metabolite, polymorph, salt, solvate, hydrate, or clathrate thereof.

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15 25. The method of claim 19 or 20 further comprising administering to a patient in need of such treatment or prevention a therapeutically or prophylactically effective amount of an antihistamine, anti-inflammatory drug, non-steroid anti-inflammatory drug, or steroid.

20 26. The method of claim 19 wherein the disease or disorder is asthma, allergic rhinitis, inflammation or chronic pulmonary inflammatory disease.

25 27. The method of claim 19 wherein the disease or disorder is chronic obstructive pulmonary disease.

28. The method of claim 19 or 20 wherein the patient is a mammal.

30 29. The method of claim 19 or 20 wherein the stereomerically pure (-)-2-[1-(3-Ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminooindoline-1,3-dione is administered parenterally, transdermally, mucosally, nasally, buccally, sublingually, or orally.

35 30. The method of claim 29 wherein the stereomerically pure (-)-2-[1-(3-Ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminooindoline-1,3-dione is administered orally.

31. The method of claim 30 wherein the stereomerically pure (-)-2-[1-(3-Ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione is administered orally in a tablet or capsule form.

5 32. The method of claim 19 or 20 wherein the therapeutically or prophylactively effective amount is from about 1 mg to about 1000 mg per day.

33. The method of claim 32 wherein the therapeutically or prophylactively effective amount is from about 5 mg to about 500 mg per day.

10

34. The method of claim 33 wherein the therapeutically or prophylactively effective amount is from about 10 mg to about 200 mg per day.

15

35. A pharmaceutical composition comprising stereomerically pure (-)-2-[1-(3-Ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione, or a pharmaceutically acceptable polymorph, prodrug, salt, solvate, hydrate, or clathrate thereof; and a pharmaceutically acceptable carrier, excipient or diluent.

20

36. The pharmaceutical composition of claim 35 wherein said pharmaceutical composition is suitable for parenteral, transdermal, mucosal, nasal, buccal, sublingual, or oral administration to a patient.

37. The pharmaceutical composition of claim 36 wherein said pharmaceutical composition is suitable for oral administration to a patient.

25

38. The pharmaceutical composition of claim 35 wherein the amount of stereomerically pure (-)-2-[1-(3-Ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione is from about 1 mg to about 1000 mg.

30

39. The pharmaceutical composition of claim 38 wherein the amount of stereomerically pure (-)-2-[1-(3-Ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione is from about 5 mg to about 500 mg.

40. The pharmaceutical composition of claim 39 wherein the amount of stereomerically pure (-)-2-[1-(3-Ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminooindoline-1,3-dione is from about 10 mg to about 200 mg.

5 41. A single unit dosage form which comprises stereomerically pure (-)-2-[1-(3-Ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminooindoline-1,3-dione or a pharmaceutically acceptable prodrug, salt, solvate, hydrate, or clathrate thereof; and a pharmaceutically acceptable carrier, excipient or diluent.

10 42. The dosage form of claim 41 wherein said dosage form is suitable for parenteral, transdermal, mucosal, nasal, buccal, sublingual, or oral administration to a patient.

15 43. The dosage form of claim 42 wherein said dosage form is a capsule or a tablet.

44. The dosage form of claim 42 wherein said dosage form is an aerosol.

20 45. The dosage form of claim 41 wherein the amount of stereomerically pure (-)-2-[1-(3-Ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminooindoline-1,3-dione is from about 1 mg to about 1000 mg.

25 46. The dosage form of claim 45 wherein the amount of stereomerically pure (-)-2-[1-(3-Ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminooindoline-1,3-dione is from about 5 mg to about 500 mg.

30 47. The dosage form of claim 46 wherein the amount of stereomerically pure (-)-2-[1-(3-Ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminooindoline-1,3-dione is from about 10 mg to about 200 mg.

48. Stereomerically pure (-)-2-[1-(3-Ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminooindoline-1,3-dione, substantially free of its (+) isomer, or a pharmaceutically acceptable prodrug, metabolite, polymorph, salt, solvate, hydrate, or clathrate thereof.

49. A method of producing a stereomerically pure enantiomer of 2-[1-(3-Ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione which comprises:

5 (a) contacting 1-(3-Ethoxy-4-methoxy-phenyl)-2-methanesulfonyl-ethylamine with a chiral amino acid under a condition sufficient to form a chiral amino acid salt of 1-(3-Ethoxy-4-methoxy-phenyl)-2-methanesulfonyl-ethylamine ; and

10 (b) contacting the chiral amino acid salt of 1-(3-Ethoxy-4-methoxy-phenyl)-2-methanesulfonyl-ethylamine with N-(1,3-Dioxo-1,3-dihydro-isobenzofuran-4-yl)-acetamide under a condition sufficient to form a final product..

50. The method of claim 49 wherein the chiral amino acid is the D isomer of alanine, arginine, asparagine, aspartic acid, cysteine, glutamine, glutamic acid, glycine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine, valine, ornithine, 4-aminobutyric acid, 2-amino isobutyric acid, 3-amino propionic acid, ornithine, norleucine, norvaline, hydroxyproline, sarcosine, citrulline, cysteic acid, t-butylglycine, t-butylalanine, phenylglycine, cyclohexylalanine, or N-acetyl-leucine.

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51. The method of claim 50 wherein the chiral amino acid salt is N-acetyl-D-leucine.

52. A stereomerically pure salt of (R)-2-(3-ethoxy-4-methoxyphenyl)-1-(methylsulphonyl)-eth-2-ylamine.

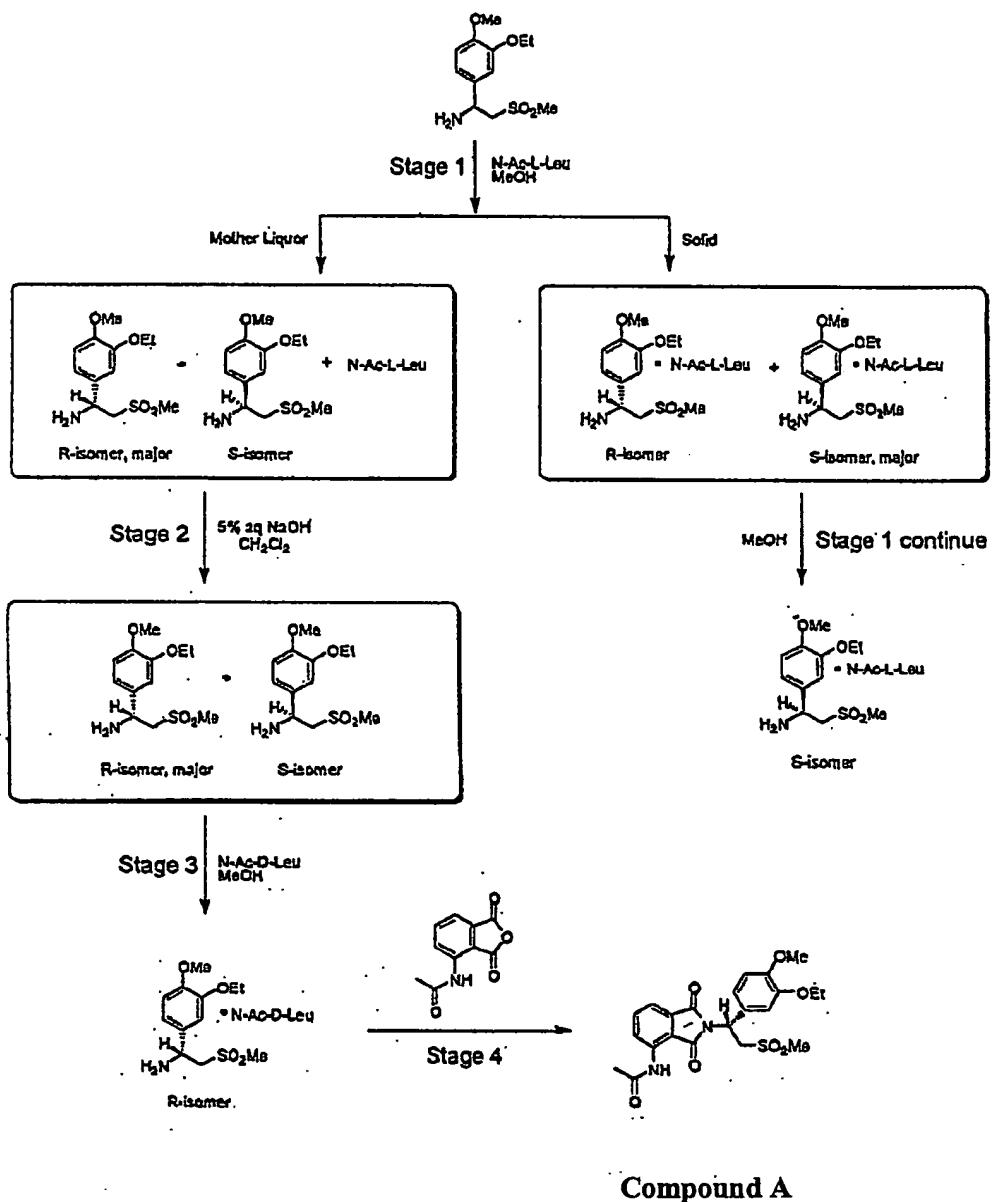
53. The stereomerically pure salt of claim 52 which is chiral amino acid salt.

30

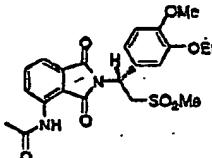
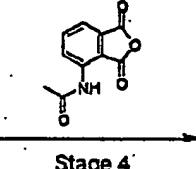
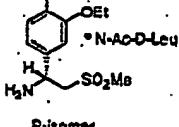
54. The stereomerically pure salt of claim 53 wherein the a salt of the D isomer of alanine, arginine, asparagine, aspartic acid, cysteine, glutamine, glutamic acid, glycine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine, valine, ornithine, 4-aminobutyric acid, 2-amino isobutyric acid, 3-amino propionic acid, ornithine, norleucine, norvaline, hydroxyproline, sarcosine,

citrulline, cysteic acid, t-butylglycine, t-butylalanine, phenylglycine, cyclohexylalanine, or N-acetyl-leucine.

55. The stereomerically pure salt of claim 54 which is a (R)-2-(3-ethoxy-
5 4-methoxyphenyl)-1-(methylsulphonyl)-eth-2-ylamine N-acetyl-D-leucine salt.



Stage 3 $\xrightarrow{\text{N-Ac-D-Leu, MeOH}}$



Compound A

FIG. 1

INTERNATIONAL SEARCH REPORT

PCT/US 03/08737

A. CLASSIFICATION OF SUBJECT MATTER
 IPC 7 A61K31/4035 C07D209/48 C07C317/28 A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
 IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

EPO-Internal, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|----------|---|-----------------------|
| X | US 6 020 358 A (MAN HON-WAH ET AL) 1 February 2000 (2000-02-01) cited in the application | 1-48 |
| Y | column 7, line 1 - line 23 column 8, line 61 -column 9, line 12 claim 1; example 12 --- | 49-55 |
| Y | AKAZOME M ET AL: "Asymmetric recognition of 1-arylethylamines by (R)-phenylglycyl-(R)-phenylglycine and its mechanism" TETRAHEDRON: ASYMMETRY, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, vol. 8, no. 14, 24 July 1997 (1997-07-24), pages 2331-2336, XP004085789 ISSN: 0957-4166 the whole document --- | 49-55 |
| | -/- | |

 Further documents are listed in the continuation of box C. Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the International filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *&* document member of the same patent family

Date of the actual completion of the international search

Date of mailing of the international search report

15 July 2003

21/07/2003

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Authorized officer

Seymour, L

INTERNATIONAL SEARCH REPORT

PCT/US 03/08737

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|----------|---|-----------------------|
| Y | LUKE G P ET AL: "Synthesis of (S)-5-(1-aminoethyl)-2-(cyclohexylmethoxy) benzamide" TETRAHEDRON: ASYMMETRY, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, vol. 10, no. 22, 19 November 1999 (1999-11-19), pages 4393-4403, XP004186385 ISSN: 0957-4166 scheme 3, step 1 ----- | 49-55 |

INTERNATIONAL SEARCH REPORT

PCT/US 03/08737

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:
— Although claims 1-34 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

The present claims do not meet the requirements of Article 6 PCT in that the matter for which protection is sought is not clearly defined. The terms "pharmaceutically acceptable prodrug and metabolite" do not enable the skilled person to determine which technical features are necessary to perform the stated function. It is thus unclear which specific compounds fall within the scope of said expressions. A lack of clarity within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search of the claims impossible. Consequently, the search does not include pharmaceutically acceptable prodrugs and metabolites of $(-)$ -2- α -(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl-4-acetylaminooxindoline-1,3-dione.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

PCT/US 03/08737

| Patent document cited in search report | Publication date | | Patent family member(s) | Publication date |
|--|------------------|----|-------------------------|------------------|
| US 6020358 | A 01-02-2000 | AU | 756308 B2 | 09-01-2003 |
| | | AU | 1447200 A | 22-05-2000 |
| | | BR | 9915201 A | 30-10-2001 |
| | | CA | 2348993 A1 | 11-05-2000 |
| | | EP | 1126839 A1 | 29-08-2001 |
| | | JP | 2002528496 T | 03-09-2002 |
| | | NO | 20012021 A | 26-06-2001 |
| | | NZ | 511253 A | 28-02-2003 |
| | | WO | 0025777 A1 | 11-05-2000 |
| | | US | 6011050 A | 04-01-2000 |